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Art and Science of Surgery*

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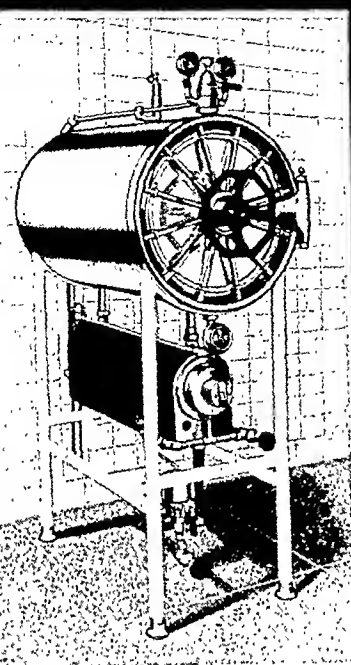
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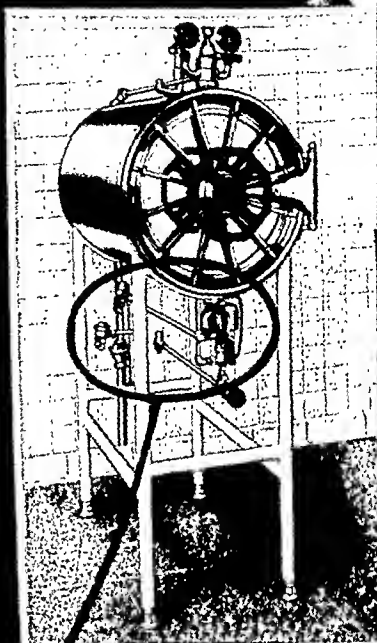
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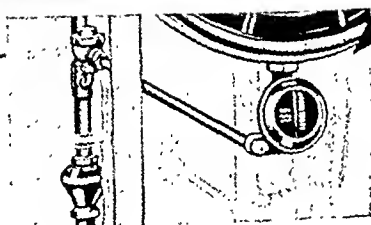
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# SURGERY

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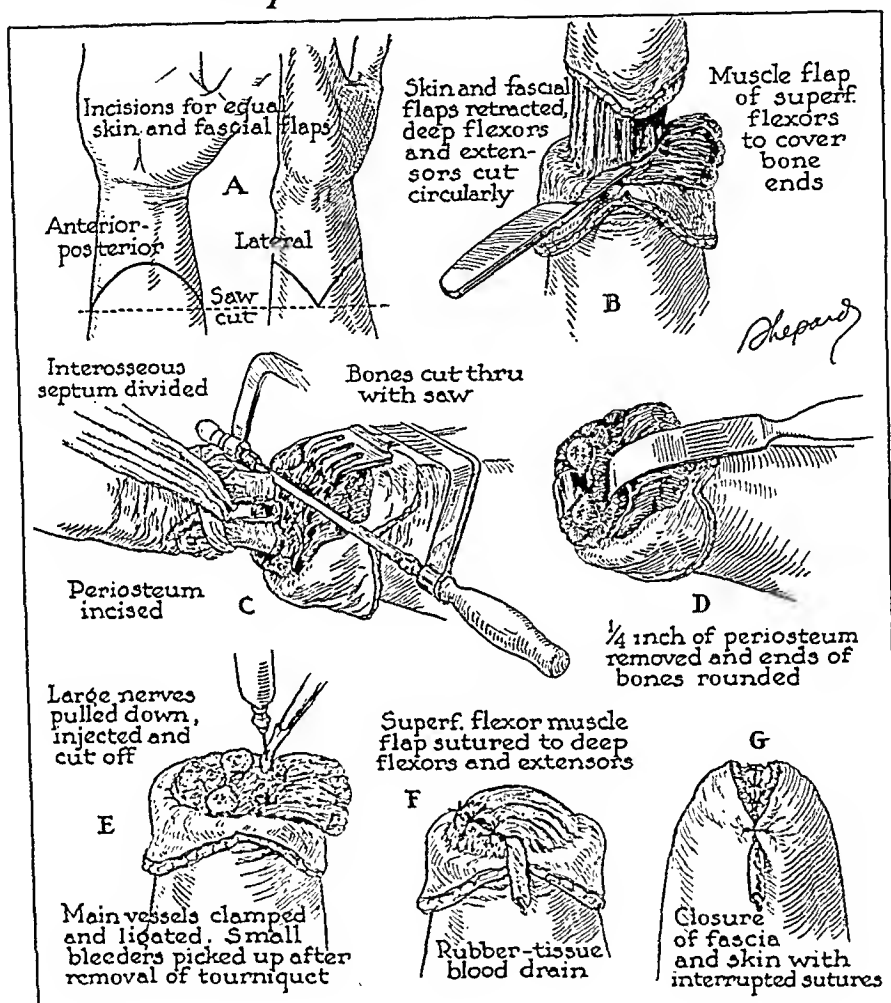
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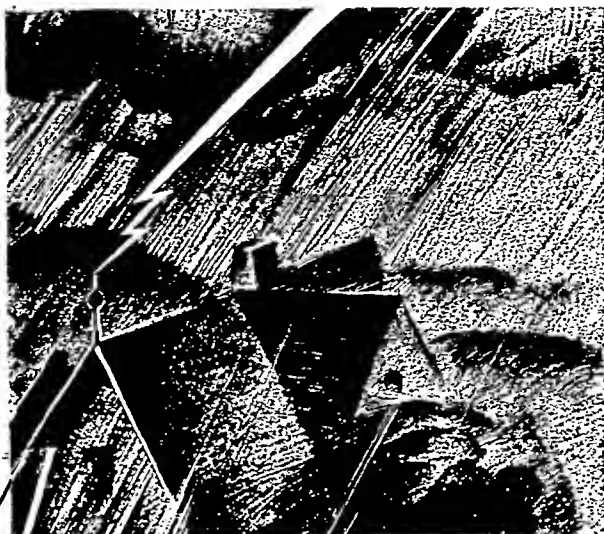
1. *Journal of the American Medical Association*, 1990; 263: 1025-1028.

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Figure 1. The effect of the concentration of the *Agrobacterium* suspension on the transformation efficiency of *Agrobacterium* strains. The number of transformed cells was determined by the number of colonies growing on the selective medium. The results are the mean of three independent experiments. Error bars represent standard deviation.

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By Hugh Hampton Young, M.D., Sc.D., F.R.C.S.I., D.S.M., Professor of Urology, Johns Hopkins University; Visiting Urologist, Brady Urological Institute, Johns Hopkins Hospital. Buckram, 6 x 9, 650 pages, 53½ original drawings by William P. Didusch, \$10.00.

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# SURGERY

VOL. 2

DECEMBER, 1937

No. 6

## Original Communications

### A REPORT ON THE VALUE OF THE IVY BLEEDING TIME TEST AND THE USE OF VIOSTEROL IN CASES OF OBSTRUCTIVE JAUNDICE

FLOYD BOYS, M.D., ANN ARBOR, MICH.

*(From the Department of Surgery, University of Michigan)*

THAT the problem of the bleeding tendency in cases of obstructive jaundice is a serious matter is appreciated when one realizes that some 50 per cent of all postoperative deaths among these patients is said to be the result of hemorrhage. Many tests have been recommended in the past for the determination of the latent bleeding tendency in jaundiced patients, but no reliable and practical one from a clinical point of view was discovered until recently. In April, 1935, Ivy<sup>1</sup> and McNealy and their coworkers announced a new bleeding time test which seemed to fulfill these requirements. In a word, the test was a modification of the old Duke test with the factor of capillary wall tonicity eliminated by means of a blood pressure cuff. Finding clinical evidence to support the hypothesis that the cause of bleeding in obstructive jaundice is due to a low liver reserve of fat soluble vitamins, McNealy<sup>2</sup> and others advocated at this time the use of viosterol for the correction or prevention of the bleeding tendency in this type of jaundice. Their clinical results were based upon observations made on 900 miscellaneous cases followed at the Cook County Hospital in Chicago and were excellent indeed. We proposed to try out both the test (now called the Ivy bleeding time test) and the use of viosterol in the cases of obstructive jaundice seen on the surgical services at the University Hospital and see whether or not their clinical results could be substantiated.

During the past year a series of 35 cases of obstructive jaundice, with and without bleeding, has been carefully followed and studied by us. Each of these patients was tested by the same individual and all clinical data were obtained and recorded by him. Specific and identical notes were kept for all cases.

Received for publication, June 21, 1937.

The following chart gives the sex, age distribution, and diagnoses of the cases studied:

SEX	TOTAL	AGE		AVER- AGE	CD OR GB STONES	PANCREATIC, OR C.D. STRICTURE, OR		
		YOUNG- EST	OLD- EST			BILIARY CARCINOMA	STENOSIS	CIRRHOSIS
Male	14	25	70	55	6 (43%)	7 (50%)	-	1 (7%)
Female	21	25	71	51	10 (40%)	9 (44%)	2 (8%)	-

## I

We were first interested in evaluating the coagulation and bleeding time factors. The normal coagulation time was considered under 5 minutes. The upper limit of normal for the Duke bleeding time was considered to be 180 seconds and that for the Ivy test 240 seconds, as determined by Ivy and McNealy. Our observations in this regard were as follows:

	CASES	ELEVATED COAG. TIME	ELEVATED DUKE B.T.	ELEVATED IVY B.T.
With bleeding	9	0	4 (44%)	9 (100%)
Without bleeding	26	0	5 (20%)	15 (60%)

In no case, it will be observed, was the coagulating time significantly elevated. However, bleeding time elevation, especially the Ivy, signified potential bleeding. In the cases with bleeding, the Duke bleeding time was elevated in 44 per cent and the Ivy in 100 per cent. In cases not presenting clinical bleeding, the Duke bleeding time was elevated in 20 per cent while the Ivy was elevated in 60 per cent. Comparing the two bleeding time tests, it is seen that the Ivy test had a prognostic value not observed with the Duke test.

## II

Having found to our own satisfaction a definite correlation between the bleeding time and clinical bleeding, we next made observations regarding the Ivy bleeding time and the jaundice itself.

	CASES	ELEVATED IVY B.T.	NORMAL IVY B.T.
With bleeding	9	9 (100%)	0
Without bleeding	21	12 (57%)	9 (43%)

This chart showed that in these cases of obstructive jaundice, with or without bleeding, the Ivy bleeding time was usually elevated.

The figures just mentioned suggested that perhaps there existed a definite relationship between the elevated Ivy bleeding time and the degree or duration of the jaundice. In a total of 30 of the cases it was possible to determine accurately the total number of weeks' duration of the jaundice in the past and present illnesses of these patients.

*Jaundiced Cases With Bleeding*

	CASE	IVY	BLEEDING		DEGREE†	JAUNDICE	
			PRESENT	LATER*		DURATION	BILIRUBIN‡
1.	GB	350	x	x	3	2 wk.	100
2.	MB	335	o	x	3	9 wk.	180
3.	JE	540	o	x	3	6 mo.	108
4.	GG	330	o	x	2	3 mo.	90
5.	EP	360	o	x	2	7 mo.	60
6.	MK	480	x	x	1	30 mo.	30
7.	IW	330	o	x	3	4 wk.	160
8.	CL	245	o	x	3	5 mo.	160
9.	HA	375	x	x	3	2 wk.	200

*Jaundiced Cases Without Bleeding*

	CASE	IVY	BLEEDING		DEGREE†	JAUNDICE	
			PRESENT	LATER*		DURATION	BILIRUBIN‡
10.	KA	450	o	o	3	2 mo.	100
11.	CT	700	o	o	2	1 wk.	55
12.	HO	360	o	o	1	4 wk.	-
13.	WE	360	o	o	1	3 mo.	15
14.	KC	460	o	o	3	5 mo.	176
15.	ES	430	o	o	1	2 days	20
16.	JK	250	o	o	1	4 mo.	70
17.	MH	195	o	o	1	4 wk.	18
18.	McM	310	o	o	1	5 wk.	50
19.	RR	200	o	o	2	6 wk.	100
20.	NC	105	o	o	2	5 mo.	80
21.	EF	175	o	o	3	2 wk.	100
22.	JD	355	o	o	3	3 mo.	220
23.	SC	400	o	o	3	2 mo.	110
24.	JW	250	o	o	3	3 wk.	120
25.	VG	200	o	o	1	4 wk.	13
26.	LAI	120	o	o	2	12 mo.	18
27.	FC	210	o	x§	2	10 wk.	50
28.	EB	170	o	o	2	2 wk.	90
29.	IE	240	o	o	1	6 wk.	30
30.	FV	300	o	o	1	3 wk.	25

\*Developing after present examination.

†This is the clinician's estimation; 1 is mild; 2 is moderate; 3 is marked.

‡All of the bilirubin tests were "direct."

§This patient developed p.o. mesenteric thrombosis with gangrene of ileum.

Cases with a lower jaundice (and bilirubin) but with a longer duration, as in Case 5, had about the same bleeding time as those with a higher jaundice and a shorter duration, as in Case 1. Granting the hypothesis of Ivy and McNealy as to the cause of bleeding in these jaundice cases, we believed that these figures indicated that the rate of depletion of the liver reserve of fat soluble vitamins varies with, and depends upon, the duration of the obstruction and upon its completeness.

## EFFECT ON THE B.T. AND BLEEDING BY THE SURGICAL REMOVAL OF THE OBSTRUCTION CAUSING THE JAUNDICE WITHOUT THE USE OF VIOSTEROL

	NAME	DAYS P.O.	IVY B.T.	BLEEDING	BILIRUBIN
1.	MB	6	450 to 260	0 to 0	181 to 65
2.	FV	9	300 to 160	0 to 0	25 to 12
3.	ES	5	430 to 150	0 to 0	20 to -
4.	IE	5	260 to 160	0 to 0	30 to 15



In 8 cases, where viosterol was not used, observations were made regarding the bleeding time and the surgical removal, or failure of removal, of the cause of the obstruction.

THE SAME EFFECTS WHEN SURGICAL REMOVAL OF THE OBSTRUCTION COULD NOT BE DONE

1.	LW	10	290 to 480	0 to x	160 to 160
2.	CL	5	245 to 360	0 to x	150 to 160
3.	GG	15	330 to —	0 to x	80 to 60
4.	NC	6	110 to 210	0 to 0	80 to 50

The surgical removal alone of the obstruction caused a progressive and rapid diminution in the bleeding time and the bilirubin. Where only a laparotomy was performed and the obstruction could not be removed (cases with extensive and progressive carcinomatosis or hepatitis), the Ivy bleeding time increased and the bilirubin did not diminish. We considered this to be more evidence that the Ivy bleeding time is related to the obstructive element in the jaundice.

### III

It was possible to follow carefully 20 cases in which viosterol was used, with or without bile salts, as recommended by Ivy and McNealy. Each of these patients was given 50 minims of viosterol (Mead, Johnson & Company) three times a day and 5 or 10 gr. tablet of ox or pig bile by mouth three times a day when the stools were acholic.

CASE	BEFORE VIOSTEROL				VIOSTEROL		AFTER VIOSTEROL			
	J.*	BL.*	BL.*	DUKE	IVY	50 M. T.I.D.	J.	BL.	BL.	DUKE
1. GB	3	100	x	600	600	3 days	4	120	xx	280
2. KA	3	100	o	180	450	6 days†	4	180	o	210
3. MB	2	180	o	120	335	6 days	3	—	o	150
4. CT	2	55	o	210	700	5 days	1	7	o	130
5. JE	3	108	o	300	540	11 days	2	60	o	220
6. GG	3	90	o	170	330	6 days	3	80	o	180
7. FV	o	20	o	—	300	8 days	o	—	o	80
8. HO	1	35	o	160	360	10 days†	1	12	o	115
9. KC	3	—	o	180	460	10 days	3	176	o	160
10. PK	o	o	o	130	350	5 days	o	1	o	180
11. WE	1	15	o	120	360	5 days	1	—	o	130
12. EP	2	60	o	360	420	7 days	3	150	x	300
						26 days†	3	180	x	—
						37 days†	2	—	o	—
						41 days†	1	70	o	—
13. ES	1	20	o	225	450	14 days*	1	—	o	60
14. JKN	2	70	o	200	280	3 days*	1	8	o	70
15. MK	2	30	x	300	480	20 days	2	34	less	360
						48 days*	2	45	less	—
16. MH	1	18	o	60	195	7 days	less	—	o	55
17. McM	1	—	o	60	310	4 days	1	50	o	160
						20 days	less	—	o	55
18. IW	3	160	o	—	330	11 days*	4	225	o	240
19. NM	o	—	o	90	270	10 days	o	—	o	60
20. EF	3	100	o	55	175	10 days	3	—	o	180

\*J.—jaundice; BL.—bilirubin, BL.—bleeding.

†This means with bile salts.

‡These were cases of carcinoma with increase in size of lesion.

It is to be observed from this chart that the use of viosterol in almost all of our cases of obstructive jaundice definitely diminished the Ivy bleeding time factor and the incidence of bleeding. In 13 cases the Ivy time was reduced to normal. In 4 cases the reduction was toward normal. In 1 case there was no change. In 2 cases there was an increase, and in both instances these patients had extensive carcinomatosis.

Rearrangement and correlation of the cases and facts just reviewed with deaths indicated that the use of viosterol has a certain prognostic value.

		IVY B.T. REDUCTION	DEATHS	DAYS VIOSTEROL	AVERAGE DAYS USED
With bleeding (8 cases)	To normal	0	0	6-17	11
	Toward normal	4	3		
	No change	0	0		
	Increased	4	4		
Without bleeding (12 cases)	To normal	7	0	3-20	10
	Toward normal	4	0		
	No change	1	0		
	Increased	0	0		

Therefore, in cases of obstructive jaundice without clinical bleeding, the prognosis was considered good when reduction of the Ivy bleeding time to or toward normal occurred after an adequate trial of viosterol. Only rarely was there an increase in the bleeding time among these patients. In obstructive jaundice cases with clinical bleeding and presenting a reduction of the Ivy bleeding time to normal with the use of viosterol, the prognosis was likewise fairly good. But, the prognosis in such cases was only fair when the bleeding time returned merely toward normal, poor when it showed no change, and fatal when the Ivy time increased. These bleeding time changes occurred, one way or the other, within a period of 7 to 21 days, the average time being about 10 days.

#### IV

Fifteen of the 35 cases died during this past year, either in or outside the hospital. In 12 of them an autopsy was obtained with the microscopic liver findings shown in the table on page 822.

It will be noted that the chief autopsy diagnoses were quite evenly divided between carcinoma and cirrhosis of the liver. May it not be argued, as a diagnostic point, that when the Ivy bleeding time does not improve in a reasonable period of time with the use of viosterol, carcinoma or cirrhosis of the liver is to be suspected as the likely cause of the supposedly permanent liver fat soluble vitamin insufficiency? Again, may it not be similarly said postoperatively that the failure to show an improved Ivy bleeding time after apparent removal of the obstruction causing the jaundice (as best as can be established by palpation and

*Clinical Cases With Bleeding\**

	CASE	HEMORR.	CA.	CIRR.	CHOL.	INTRA-H.	PERI-H.	AT-ROPHY	FATTY	OBST. J.
1.	CL	x	(X)	o	x	x	o	o	o	x
2.	IW	x	o	(X)	x	x	o	o	o	x
3.	EP	x	o	o	(X)†	o	o	o	o	x
4.	GB	x	(X)	o	o	o	o	x	x	x
5.	HA	x	o	(X)	o	o	o	o	o	x
6.	MK	x	o	(X)	x	o	x	o	o	x
7.	JE	x	(X)	(X)	o	o	o	o	x	x

(7 out of 9 deaths, all with autopsy)

*Clinical Cases Without Bleeding*

1.	RR	x	x	(X)	o	o	o	o	x	x
2.	JW	o	(X)	x	o	o	o	o	o	x
3.	FG	o	o	(X)	o	o	o	o	x	x
4.	EF	o	(X)	o	o	o	o	o	o	x
5.	LN	x	o	(X)	o	o	x	o	x	x

(6 out of 26 cases, one without autopsy)

\*Hemorr—hemorrhages; Ca—carcinoma; Intra-H—intrahepatic cholangiolitis; Peri-H—perihepatitis; Fatty—fatty infiltration or (X) degeneration chief diagnosis; Cirr—cirrhosis; Chol—cholangitis; x—minor findings at autopsy; †—inflammatory stenosis.

probing of the common duct, and possibly after operative biliary tree lipiodol x-ray films), suggests the presence of carcinoma or cirrhosis of the liver?

## CONCLUSION

In conclusion, we feel that the above evidence lends support to the hypothesis of Ivy, McNealy, and others, regarding the cause of bleeding in obstructive jaundice and to their observations that this bleeding tendency can be prevented or corrected, when permanent liver vitamin insufficiency does not exist, by the administration of an excess of fat soluble vitamins in the form of viosterol. Viosterol administration has a definite prognostic value when correlated with the Ivy bleeding time. Our own observations indicate that this liver vitamin depletion depends upon the duration and the degree of the jaundice, and they stress the value of a careful history in this regard. Finally, we have found the Ivy bleeding time determination a simple and practical clinical test for the detecting of latent bleeding tendencies and for prognosticating about the bleeding course in cases of obstructive jaundice.

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## SPLENECTOMY

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ALTHOUGH splenectomy was done in at least a few instances before the birth of Christ,<sup>13</sup> Spence Wells, in 1865, was probably the first to perform the operation in modern times.<sup>25</sup> In the early years the mortality was high so that the operation was seldom performed. Within the last quarter of a century, however, splenectomy has become a well-recognized and justified procedure. While today it is not to be entrusted to the occasional operator, yet in the hands of a well-trained surgeon the mortality of splenectomy approaches that of any other upper abdominal surgery and depends largely upon the type of cases selected for operation.

The vast majority of patients requiring splenectomy suffer from one of three diseases—splenic anemia (Banti's disease), hemolytic jaundice, or purpura hemorrhagica. There are, however, a number of less common conditions which require removal of the spleen. Splenectomy will be discussed in its relationship to these various diseases and fifty-three cases will be reported. The cases in this series have been divided according to diagnosis in Table I.

TABLE I  
SPLENECTOMY CASES

DISEASE	NO. CASES	DIED
1 Splenic anemia (Banti disease)	21	8
2 Hemolytic jaundice	12	0
3 Purpura hemorrhagica	7	0
4 Ruptured spleen	5	0
5 Subacute bacterial endocarditis with splenomegaly	2	1
6 Multiple lymphogenous cysts	2	0
7 Syphilitic splenomegaly	1	0
8 Primary tuberculosis of the spleen	1	0
9 Myelogenous leukemia	1	0
10 Aplastic anemia	1	1
	53	10 (18.8%)

### SPLENIC ANEMIA—(BANTI'S DISEASE)

In 1894 and again in 1910, Banti described a syndrome which has since been associated with his name. He suggested splenectomy as the treatment of choice.<sup>37</sup> The syndrome is characterized by a progressive enlargement of the spleen associated with a persistent anemia. There is a marked tendency toward gastrointestinal hemorrhage. In the terminal stage there is cirrhosis of the liver followed by ascites and

Received for publication, June 14, 1937.

TABLE II  
SPLENIC ANEMIA—21 CASES

NO.	NAME	SEX	AGE	LIVER DAMAGE		PRETHERAPEUTIC HEMOGLOBIN	FOL-LOWED	RESULT
				CLINICALLY	AT OPERATION			
1	P. B.	M	40	No	No	45	-	Died, bronchopneumonia
2	E. D.	F	49	Jaundice	Severe	43	-	Died
3	P. L.	M	49	Ascites	Severe	72	-	Died, gastric hemorrhage
4	L. S.	M	42*	Jaundice and ascites	Severe	-	-	Died, gastric hemorrhage
5	A. B.	F	14	Ascites	Severe	-	-	Died, gastric hemorrhage
6	J. C.	M	24	Jaundice and ascites	Severe	80	-	Died, "liver insufficiency"
7	J. L.	M	34	Jaundice	Severe	78	-	Died, "liver insufficiency"
8	P. C.	M	52†	No	Severe	48	-	Died, "liver insufficiency"
9	P. C.	F	62	No	Enlarged	55	11 yr.	Well
10	B. S.	F	13	No	-	70	7 yr.	Hemoptosis before and after operation
11	J. G.	M	15	No	-	42	7 yr.	Hemoptosis before and for 4 yr. after operation; now well
12	C. B.	M	35	No	-	68	4 yr.	Well, still moderate anemia
13	L. D.	F	50	No	-	?	5 yr.	Well, Hb. 96%
14	M. S.	F	9	No	-	20%	5 yr.	Well, Hb. 94%
15	H. K.	F	20	No	Severe	76	3 mo.	Symptomatically improved, Hb. 76%; platelets, 170,000
16	S. F.	M	45	No	-	-	1 yr.	Well, Hb. 76%
17	J. K.	M	23*	Ascites	Severe	-	-	
18	J. S.	M	8	No	-	47	3 yr.	Well, Hb. 96%
19	J. F.	F	62	No	Severe	72	7 mo.	Improved
20	W. C.	M	55	No	Liver enlarged	55	3 mo.	Improved
21	E. S.	F	8		Liver enlarged	-	0	

\*Omentopexy done in addition to splenectomy.

†Ligation of left gastroepiploic artery.

perhaps jaundice. Very little had been added to the knowledge of the true nature of the disease since Banti's descriptions so that the diagnosis today is still largely one of exclusion. Because of this fact, it is undoubtedly true that while the patients grouped under the diagnosis of Banti's disease present common characteristics there may be different etiologic factors involved.<sup>2, 37, 38</sup>

The treatment of choice in this syndrome continues to be splenectomy. Many feel that splenectomy is worth while only in the early case and that patients who present signs of severe liver damage should not be subjected to the procedure.<sup>4</sup> It has been suggested that ligation of the splenic artery be used in these late cases and good results have been reported.<sup>47</sup> Omentopexy has been done along with splenectomy in those

cases having ascites. Because gastrointestinal hemorrhage is a major threat in many instances, the coronary vein has been ligated at the time of splenectomy.

The series of cases reported from the Mayo Clinic in 1931 included 167 cases with a mortality of 9.6 per cent. Eighty of these were still living, while 63 were well. Of those already dead, 10 lived for more than nine years. The longest survival was nineteen years. Such results certainly seem to justify the operation. Gastrointestinal hemorrhage was the direct cause of death in one-third of the patients who died after leaving the hospital.<sup>13, 32</sup>

Because of the marked difference in the operability of a patient in the early stages and a patient in the late stages of Banti's disease, it is obvious that the mortality can be regulated by the selection of the cases. There were 21 patients in this series diagnosed as Banti's disease. Seven of the group showed evidence of severe liver damage before operation; 6 of these 7 patients died. Of the 14 patients who did not show evidence of severe liver damage before operation, only 2 died. Both of these patients were found to have severely damaged livers at operation. Thus there were 8 deaths in this series; 3 caused by gastric hemorrhage, 1 by bronchopneumonia, while in 4 instances the cause was unknown. These last were spoken of as "liver deaths."

The results following splenectomy for splenic anemia depend to a great degree upon the stage of the lesion. In Table II may be seen the results of the cases in this series. The longest survival to date is eleven years. There are three patients perfectly well, with over 90 per cent hemoglobin from three to five years after operation.

#### HEMOLYTIC JAUNDICE

Hemolytic jaundice has long been divided into the congenital and acquired forms. There is some doubt, however, that the disease is ever acquired.<sup>45</sup> When the disease is first noticed after childhood and is not associated with a family history, it is usually spoken of as acquired. Under such circumstances the disease is frequently most severe.<sup>48</sup>

When normal red blood cells are placed in hypotonic salt solution, they become more globular as they increase in volume and finally rupture. The cells in hemolytic jaundice are already partially changed in that direction. Thus Haden<sup>15</sup> has demonstrated spherocytosis which causes the cells to have a smaller diameter (microcytosis), whereas, the volume is normal or increased. This phenomenon explains in part the characteristic increase in red blood cell fragility found in this disease.

In addition to these findings, there is usually a greenish pallor to the skin, with an increased Vandenberg reaction. There is a normal or increased amount of bile in the stool. There are abnormal quantities of urobilin and bilirubin in the urine. There is a secondary anemia with its accompanying increased reticulocyte count. The spleen is enlarged and usually palpable.<sup>5</sup>

TABLE III  
HEMOLYTIC JAUNDICE

NO.	NAME	SEX	AGE	DURATION OF SYMPTOMS	FRAGILITY	PEROP- ERATIVE HR.	F. U.*	GENERAL CONDITION	BLOOD
1	G. M.	M	17	8 yr.	.525-.400		2 yr.	Well	Normal
2	B. M.	F	18	3 yr.	.625-.400		3 mo.	Well	
3	E. H.	M	20	2 yr.	.725-.425		2 yr.	Well	Normal Hb. 100%
4	L. M.	F	28	--	.750-.425	33%	1 yr.	Well	R.B.C. 4,300,000 Hb.—82% P.—148,000 Jaundiced
5	T. L.	M	30	3 yr.	.500-.400	30%	1 yr.	Unim- proved, continued jaundiced	
6	M. W.	F	56	--	.500-.400		1 yr.	Well	Hb.—80% P.—normal
7	C. L.	M	22	6 yr.	?		1 yr.	Well	
8	A. M.	F	4	4 yr.	.675-.400		3 yr.	Well	
9	R. M.	M	9	5 yr.	.650-.450	22%	3 yr.	Well	
10	E. M.	F	11	1 yr.	.625-.375	70%	3 yr.	Well	
11	N. G.	M	20 mo.		.625-.450	63%	Recent		
12	E. S.	M	18	6 yr.	.525-.400	--	-		

\*Follow-up examination.

Splenectomy was first performed for hemolytic jaundice by Spencer Wells in 1887. The patient was still alive when last reported in 1932.<sup>4</sup> This operation, used empirically and found to be successful, has stood the test of time. When the diagnosis is certain, a complete and permanent cure can be expected to follow splenectomy. In the atypical case, the result may be unsatisfactory.<sup>44</sup>

It has been pointed out that although in a state of chronic anemia due to continued hemolysis, many of these cases go along for years moderately comfortable, so that one should consider the surgical mortality before advising operation.<sup>17</sup> Since the operative mortality in these chronic cases has been reduced to a minimum, it is felt that splenectomy should be advised in all typical cases unless contraindicated.

In the 12 cases in this series there were no deaths. In the 118 cases reported from the Mayo Clinic, the mortality was only 3.4 per cent.<sup>32</sup> A mortality in this neighborhood can generally be expected in chronic cases. The results following operation frequently border on the dramatic. The jaundice may disappear in a few days and the blood count may return to normal in a few weeks. The red blood cell fragility may approach but never return to normal.

Of the 12 cases in this series, only 1 has been a failure. It was recognized as being atypical at the time of operation. This patient has since been reported in detail by Hamburger and Bernstein<sup>16</sup> as a case of chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria. In about one-half of the patients in this series, the follow-up period has been quite short. The results are given in Table III.

The reports in the literature are good in a high percentage of cases. Several authors<sup>10</sup> have reported cases with recurrent jaundice. It is probable that these were cases atypical in type or with accessory spleens. In the Mayo Clinic series<sup>32</sup> of 98 cases, 82 were cured, 12 improved, and 4 unchanged. It is the consensus of opinion that if the patient presents a typical picture of hemolytic jaundice, one may expect complete and permanent relief in a high percentage of cases following splenectomy.

It has long been the teaching that splenectomy should not be performed during an acute exacerbation of the disease. All agree that it is safer to operate during a quiescent period. However, the acute exacerbation may be so severe that one is forced into some life-saving measure. Under such conditions, a blood transfusion is frequently hemolyzed regardless of the care of cross agglutination tests. Because of the fear of posthemolytic anuria, transfusions should be reserved until after splenectomy.

Doan, Curtis, and Wiseman<sup>6</sup> believe that splenectomy is the procedure of choice in the acute hemolytic crisis, whether it is spontaneous or due to some precipitating factor. They were forced into operation in 5 acute cases when the red cell count was in the neighborhood of one million. They found that the red cell count rose about one million while the patient was on the table. Studies in blood volume led them to believe that this was due to a contraction of the spleen.

#### PURPURA HEMORRHAGICA

Splenectomy was first suggested for purpura hemorrhagica in 1916 by Kaznelson.<sup>19</sup> The results in his cases were so remarkable that the operation was immediately adopted by most surgeons. Although the spleen has not been definitely proved to be the seat of the disease in purpura hemorrhagica, its removal has been followed by results justifying the continuation of the procedure on an empiric basis.

The establishing of a positive diagnosis is of paramount importance before splenectomy is considered. The disease is characterized by (1) petechial ecchymosis and bleeding from the mucous membranes, (2) low platelet count, (3) prolonged bleeding time, (4) normal coagulation time, (5) delayed or absent clot retraction, (6) a secondary anemia with evidence of regeneration, (7) a normal or increased total white count with a normal differential count, (8) a tourniquet test that may be positive, (9) the spleen that may or may not be palpable. Errors in diagnosis are most frequently made in cases of acute leukemia or aplastic anemia associated with hemorrhagic phenomenon.

Purpura hemorrhagica as it confronts the clinician may be divided into four groups:

*Group 1. Mild or Moderate Bleeding in the Initial Attack.*—There is probably universal agreement that patients in this group should be



TABLE IV  
PURPURA HEMORRHAGICA

NO.	NAME	SEX	AGE	ATTACKS	SEVERITY	DURATION	PREOPERATIVE BLOOD	F.U.	CONDITION AND BLOOD
1	M. T.	M	20	Repeated	Mild	10 yr.	P—12,800	5 yr.	
2	R. V.	M	2	Initial	Moderately severe	2 wk.	P—12,000	4 yr.	No recurrence, Hb. 94%, P—448,000
3	E. S.	F	6	Initial	Moderately severe	3 wk.	P—9,600	1 yr.	No symptoms, Hb. 76%, P—50,000
4	G. B.	F	19	Repeated	Severe exacerbation	6 mo.	P—17,600 Hb.—32%	1 yr.	No symptoms, Hb. 86%, P—250,000
5	J. R.	M	20	Repeated	Moderate	1 yr.	P—7,000 Hb. 64	2 yr.	Well, Hb. 96%
6	J. S.	M	11	Recurrent		9 yr.	Hb. 45	No F.U.	
7	C. L.	F	11	Initial attack	Severe	4 da.	Hb. 38 P—12,000	No F.U.	

treated conservatively by adequate diet, elimination of foci of infection, and transfusions if necessary. Under such treatment the majority will get well and stay well.<sup>14</sup>

*Group 2, Mild or Moderate Bleeding in a Recurrent Attack.*—There is almost universal agreement that patients in this group, having given no response to conservative therapy, should be subjected to splenectomy.<sup>8, 42, 44, 48</sup> Some feel that splenectomy should be reserved for the fulminating case with uncontrollable hemorrhage, or for the recurrent case sufficiently severe to interfere with normal growth.<sup>24</sup>

*Group 3, Severe Bleeding in the Initial Attack.*—The opinion differs as to the treatment of patients in this group. On the basis of collected cases, Whipple<sup>48</sup> and Spence<sup>42</sup> advise against splenectomy in the acute attack. The mortality in the 35 cases reported until 1932 was 34.3 per cent.<sup>7</sup> This, however, was due largely to the high mortality in the early cases. In the last 21 cases after experience had shown that greater care had to be taken as to the pre- and postoperative treatment, the mortality was only 13.6 per cent. Pemberton<sup>33</sup> probably expresses the feeling of the majority when he points out that if the bleeding cannot be controlled by packing and transfusions, early operation is indicated. The high mortality in the acute cases will be found in those cases where operation has been postponed until one is forced into splenectomy as a last resort.

*Group 4, Severe Bleeding in a Recurrent Attack.*—These patients have previously demonstrated their ability to go into remission. For this reason they should be treated by transfusion and given every opportunity to again go into remission. However, the patient must not be allowed to get in poor condition before the decision is made to resort to splenectomy.

Many nonoperative forms of treatment have been suggested for purpura hemorrhagica, such as a high vitamin diet,<sup>13, 18</sup> thromboplastic injections,<sup>18</sup> antivenom injections,<sup>12, 30, 43</sup> nonspecific protein shock,<sup>9, 28</sup> and ovarian extract in menstrual purpura.<sup>21</sup> Although x-ray therapy has received relatively little encouragement,<sup>29</sup> excellent results have recently been reported in a short series of cases.<sup>39</sup>

The results following splenectomy for purpura hemorrhagica have been sufficiently satisfactory so that one is justified in advising operation in any case where the disease is an inconvenience and has not responded to conservative measures. According to the published reports up to 1932,<sup>7</sup> 87 per cent of 179 followed cases were cured. There was, however, an admittedly short follow-up in many instances. In the Mayo Clinic series<sup>33</sup> with long follow-up periods, 63 per cent were permanently cured. In only one instance, however, was the recurrent bleeding of a serious nature. Other reports continue to be favorable in a high percentage of cases.<sup>1, 35, 45</sup> Griffin,<sup>13</sup> with a large experience, states that he has never seen purpura persist after splenectomy and a conscientious elimination of foci of infection. It has been suggested<sup>26</sup> that accessory spleen may account for many cases of apparent cures followed by recurrence.

The 7 cases of purpura hemorrhagica reported in this series are shown in Table IV. On an incomplete follow up only 1 patient had had any recurrent bleeding and this consisted of 2 insignificant nose bleeds in 5 years.

#### RUPTURED SPLEEN

Rupture of the spleen is usually the result of violent trauma. It occasionally occurs spontaneously.<sup>52</sup> When the diagnosis is made, it is safest to operate as soon as the patient is in condition, even though the hemorrhage has apparently stopped, because of the danger of delayed or recurrent hemorrhage.<sup>23</sup>

In this series there were 5 cases of ruptured spleen, all due to severe trauma. The patients have been followed from one to eleven years. All of these patients are perfectly well and have noticed no ill effects from the loss of the spleen. The cases are given in Table V.

TABLE V  
RUPTURED SPLEEN

NO.	NAME	AGE	FOLLOW-UP	GENERAL HEALTH	BLOOD STUDIES
1	E. E.	25	11 yr.	Excellent	R.B.C.—4,800,000 Hb.—90%
2	R. S.	6	4 yr.	Excellent	R.B.C.—4,000,000 Hb.—72% P—576,000
3	E. R.	14	1 yr.	Excellent	--
4	A. D.	12	5 yr.	Excellent	--
5	M. B.	55	2 yr.	Good	--

Removal of the normal mammalian spleen was found by Krumblhaar<sup>20</sup> to cause a mild temporary anemia, with an increase in the resistance of the red blood cells. Gottlieb<sup>41</sup> has advanced the theory that the spleen is normally active in iron metabolism so that the iron is not retained and utilized following its sudden removal. Thus a temporary anemia is produced until the other parts of the reticuloendothelial system gradually take over this function of the spleen. He was able to decrease the severity of this transitory anemia by feeding iron.

#### UNCOMMON CONDITIONS

There are several other conditions for which a patient is occasionally subjected to splenectomy which happen to be represented in this series.

Splenectomy was performed twice in this series upon patients with subacute bacterial endocarditis with splenomegaly. One had a splenic abscess. This patient died one week after operation from a cerebral hemorrhage. The other patient was not followed. Riesman, Kolmer, and Palowe<sup>36</sup> have reported 4 cases of splenectomy for subacute bacterial endocarditis and feel that life is prolonged and made more comfortable by the operation.

Multiple lymphagenous cysts of the spleen was the diagnosis in two cases. Both of these cases have completely recovered and have normal blood counts two and four years after operation. In one instance, a 3,400 gm. spleen was removed from a 100 pound, twenty-year-old woman.

Splenomegaly is occasionally associated with a case refractory to antisyphilitic treatment. Splenectomy is then indicated as a part of the antisyphilitic treatment. One such case was included in this series, a seventeen-year-old boy with congenital syphilis. Following splenectomy he responded satisfactorily to treatment.

Primary tuberculosis of the spleen has been reported in 51 instances up until 1912 according to Winternitz.<sup>50</sup> Since that time a somewhat smaller number have been added to the literature. A positive preoperative diagnosis has been made only in those cases where calcification of the spleen was demonstrated by x-ray.<sup>41</sup> Isolated healed tubercles have been found in the spleen on autopsy, but such spleens were normal in size. When a primary tuberculosis of the spleen has assumed the magnitude of a clinical splenomegaly, the prognosis is probably hopeless without surgery. The diagnosis is to be considered in a case of splenomegaly of unknown origin with fever, loss of weight, and lassitude. There may be a close similarity to splenic anemia.<sup>3, 34, 40</sup> When splenectomy is done before other tuberculous foci become established, the results are uniformly good. In our case, the patient, aged fifty-one years, had lost forty pounds in weight in eighteen months. The spleen weighed 2,100 gm. All other studies were negative, except for a moderate anemia. Following splenectomy the patient

regained his normal weight and has been perfectly well for two years. His red cell count is now 4,800,000 and his hemoglobin is 98 per cent.

Splenectomy was done for myelogenous leucemia only once in this series. The patient died three months after operation. Griffin<sup>43</sup> feels that if there is no evidence of acute leucemia, if the history is short, and if there is no marked anemia, splenectomy is justifiable after pre-operative irradiation. In the 43 cases reported by him, 20 were well for two years, while 3 were well over five years.

This series contains one case of aplastic anemia that was associated with purpura. Splenectomy was done as a last resort after six months of conservative treatment. There was no response of the bone marrow, and the patient died on the eighth postoperative day.

#### TECHNIQUE

The operation of splenectomy may be a very difficult one or a relatively simple one, depending upon the size of the spleen and the presence or absence of adhesions. The left rectus incision is probably most frequently used. The lower pole of the spleen is delivered first and brought out of the wound. The upper pole of the spleen then may be exposed. By using this procedure, the size of the incision need not be so large as would otherwise be required. When the spleen is very large, it may occasionally become necessary to make a lateral transverse extension of the incision at the lower end. This gives considerable additional exposure. Such a step is seldom required but may be a valuable aid when an especially large spleen is encountered. Some surgeons find the left paramedian<sup>40</sup> or the left subcostal<sup>31</sup> incision preferable to the left rectus incision.

By means of the gloved finger, the spleen is freed posteriorly. In this manner the capsule is not torn. The lienorenal ligament may occasionally have to be nicked with an instrument. The lower pole of the spleen is separated first and brought out of the incision. As this is done, the upper part of the spleen can be exposed. When the posterior attachment has been completely freed, the spleen is turned up to expose the posterior aspect of the pedicle devoid of a peritoneal covering. The peritoneum is then slit over the anterior aspect of the pedicle and the splenic vessels are exposed. Care must be taken that the tail of the pancreas, the stomach, and the retroperitoneal duodenum are sufficiently pushed aside before hemostats are applied. The vessels are clamped close to the spleen, which is then removed. The vessels are doubly ligated. Wise<sup>41</sup> has suggested the use of a rubber-shod clamp across the entire pedicle until the vessels are ligated individually. It would seem that he has minimized the possibility of damage to the pancreas by this procedure. The oozing from the bed of the spleen is usually so insignificant that no drainage is necessary. When the

ooze is sufficient, a Penrose drain may be inserted. The drain is best brought out through a stab wound lateral to the incision.

When a large spleen has been removed, an abdominal binder is applied immediately to help maintain abdominal pressure. Pitressin is given every fourth hour for the first forty-eight hours. The convalescence may be marked by a moderately febrile course which is frequently quite prolonged.<sup>27</sup> This is probably due to a thrombophlebitis of the splenic vein as mentioned by Bryce.<sup>2</sup> No deaths due to extension of the thrombosis into the portal vein have been recognized in this series.

#### SUMMARY

1. A series of 53 splenectomies is reported, with a gross mortality of 18.8 per cent. The late cases of Banti disease with clinical evidence of severe liver damage (ascites or jaundice) were responsible for the greater part of the mortality. If these cases were eliminated from the series, the mortality would be 8.6 per cent. There were no deaths in 19 cases of hemolytic jaundice and purpura hemorrhagica.

2. The results to be expected in the various conditions following splenectomy are discussed.

3. A case of primary tuberculosis of the spleen is reported.

4. The technique of splenectomy is discussed.

#### CONCLUSIONS

1. Splenectomy in splenic anemia (Banti disease) had best be confined to the early stages. Splenectomy is justified in the late stages only when the discomfort due to the size of the spleen makes life miserable for the patient.

2. Splenectomy is the treatment of choice in hemolytic jaundice. It is preferable to perform the operation during a remission, but occasionally it is necessary to remove the spleen during an acute exacerbation. The results following splenectomy are good in a high percentage of cases.

3. Cases of chronic hemorrhagic purpura that do not respond to conservative therapy should be subjected to splenectomy. In acute purpura hemorrhagica, if the bleeding does not respond promptly to conservative measures, splenectomy should be performed early before the patient's condition is critical. A careful elimination of infection is important in the prevention of recurrent purpura. Recurrence of a serious nature is unusual.

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## ABNORMAL PROMINENCE OF THE EARS: A METHOD OF READJUSTMENT

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### INTRODUCTION

AT ONE time or another, every surgeon is asked what can be done to restore projecting ears to normal position. This problem is one that quite frequently has been brought to us for solution, and we have found that the solution is not quite as simple as it may seem at first glance. In addition to the correction of the actual deformity, we have to deal with the psychologic aspect of the question, both from the standpoint of the patient, and frequently from that of the parents as well. For this reason in children, we often replace congenitally prominent ears into normal position before they begin school in order to avoid the distressing mental effect caused in so many instances by the gibes and cruel remarks of the other children.

We have in our series a number of cases where the replacement of prominent ears has wrought a complete change in the mental complex of the child and has been the beginning of a new and happy life.

In older patients, the results for the better are sometimes psychologically astounding, since many of them had been unaware that anything could be done to correct the deformity and had gone on in life trying to hide their feelings, or had appeared in public as infrequently as possible.

There is a group, however, who are unaffected psychologically, but who come for help principally for practical reasons: aviators who cannot comfortably wear their snug helmets; young women who are unable to wear the tight hats which the fashion of the moment may call for. To this group may be added those who cannot get suitable employment on account of the odd appearance caused by widely outstanding ears.

The external ear is formed during the sixth week of fetal life from six tubercles which appear on the mandibular and hyoid arches around the first cleft depression and also from the elevation of the skin behind the tubercles on the hyoid arch. The ear begins to assume a definite form during the latter part of the second and the first part of the third month. The margin of the ear at the posterior superior angle is pointed (Darwin's tubercle) and because the crura of the antihelix are unformed, the ear protrudes from the head. About the sixth fetal month, the margin curls, forming the helix, the antihelix becomes more definitely folded,



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and its crura appear. When completely formed, the normal ear rests at an angle of about  $30^\circ$  to the head. The lower portion of the antihelix is usually well developed; in some instances the superior crus is present; and in some both crura are present, but the folding of the cartilage

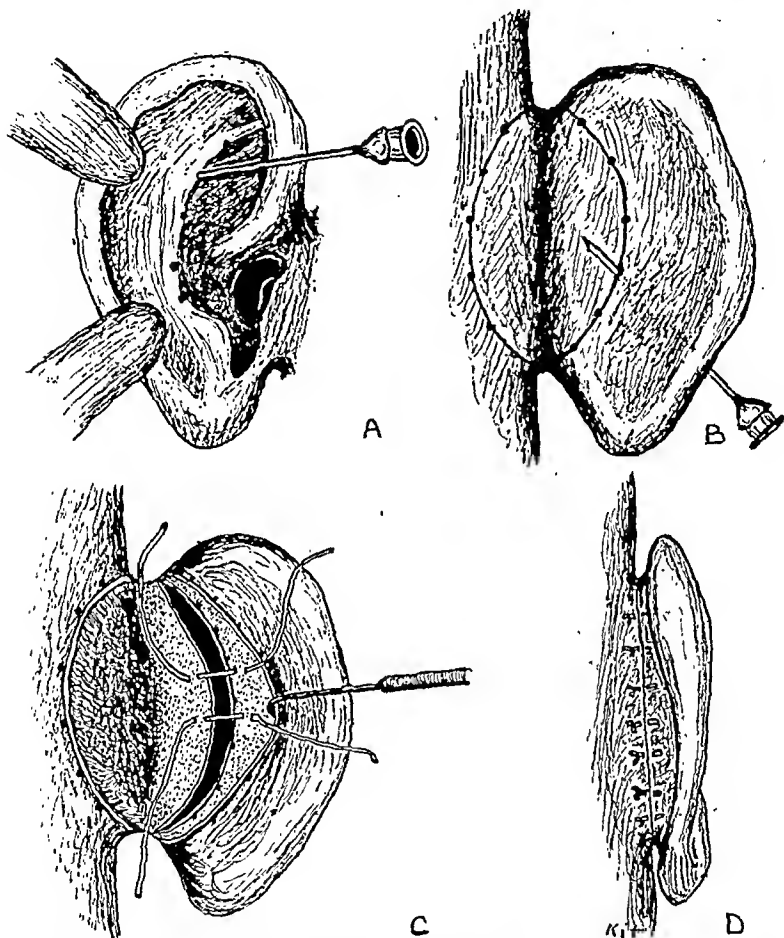


Fig. 3.—Schematic drawings showing the steps in the operation for the replacement of prominent ears. A, The ear is placed in its normal position against the head and the upper and posterior limits are marked on the scalp with an hypodermic needle dipped in brilliant green, 5 per cent in alcohol. Note two punctures above the ear and one behind. With the ear in this position the undeveloped antihelix will reform sufficiently to indicate the line of proposed reconstruction. Along this line with an hypodermic needle dipped in the brilliant green solution, punctures are made completely through the ear and about 1 cm. apart. B, Shows the puncture marks and the needle emerging on the posterior surface of the ear through one of them. The needle shown in the drawing is comparatively much larger than that actually used which is 24 gauge and 1 inch long. The points of perforation are connected with a line of brilliant green and while the solution is still damp the ear is pressed against the head and a contact line is made. This line is freshened with the green solution and the ends are carried forward and joined, making an elliptical-shaped pattern. The area of skin thus outlined is that which is to be removed. C, The skin has been removed. The marks of the perforations in the skin can be seen. The second line of green-stained dots are those left in the cartilage by the needle punctures through the ear. The area from which the cartilage was excised, which conforms to the curve of these perforations, is shown. The cartilage spring has been broken. Two sutures of catgut of the type used to turn in the cartilage edges to form the antihelix can be seen placed in the perichondrium. D, The ear assumes normal position and the skin is closed with on-end mattress sutures of horsehair.

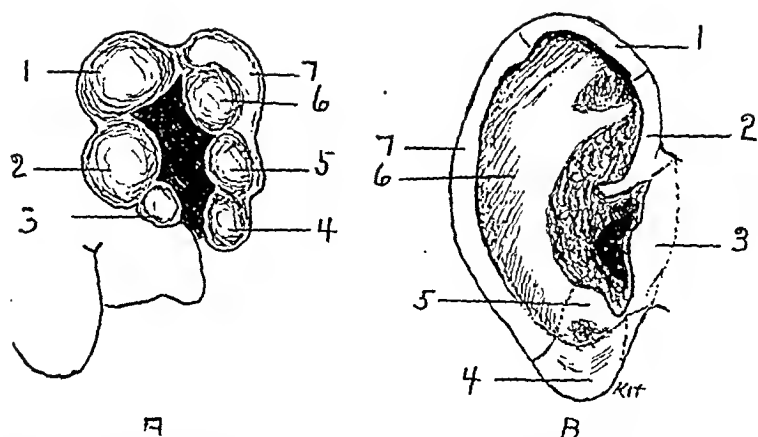


Fig. 1.—Schematic drawings to show the embryology of the ear. A 1, 2, 3, Tubercles which arise from the first mandibular arch to form the tragus, B 3; crus of the helix, B 2; and helix, B 1. A 4, 5, 6, Tubercles which arise from the hyoid arch to form the lobe, B 4; antitragus, B 5; anthelix, B 6. A 7, Skin elevation behind the tubercles of the hyoid arch which form the descending helix or posterior margin of the ear B 7.

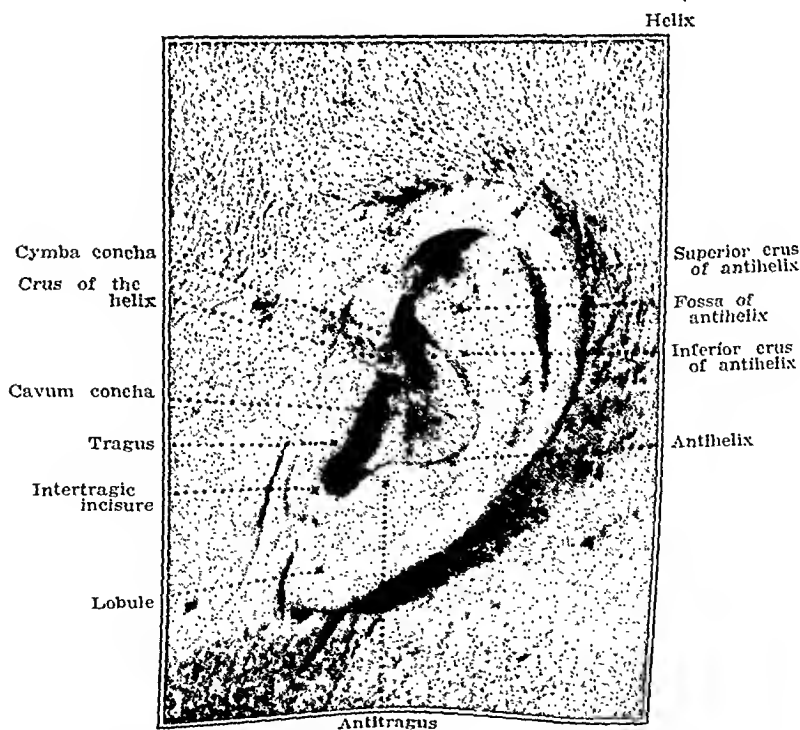


Fig. 2.—Photograph of an ear in normal position with a well-developed anthelix and its crura. Note the strong supporting ridges.

known. There is normally a sharp ridge of cartilage between the concha and the fossa above and behind the antihelix, and if this supporting ridge is missing, the deformity results. In other words, in the majority of cases the incomplete development of the antihelix, especially of the crura, is the principal cause of the projecting ears.

Abnormal prominence of the ears is usually congenital, especially in the marked cases, but it is possible that they may be acquired by young children constantly sleeping with the ear curled up, or by having the ears frequently rolled forward under carelessly placed caps.

We have noted in a number of instances that heredity seemed to be a definite factor. The deformity is usually bilateral, but may be unilateral. Sometimes the prominence is more marked on one side than on the other,



Fig. 4D.—See opposite page for legend.

and the actual deformity of each ear varies. Sometimes the ears are of different sizes and are not on the same level. Ordinarily hearing is not affected by the prominence of the ears.

Abnormally prominent ears may be divided into two general groups: first, where the ear itself is of normal shape but is attached to the head in an abnormal position; second, where the prominence is due to an abnormality of the ear itself. In both of these types the ears may be enlarged, but in the second group we frequently find that when the unfolded cartilage is readjusted, the ear which was apparently enlarged assumes the normal size.

We also find in the first group that ears which seem much too large when in the abnormal position are inconspicuous in regard to size when the angle is changed and when they are placed closer to the skull. Con-

has not been sufficient to support the ear normally close to the head. In some instances, both erura are completely unfolded and give no support at all.

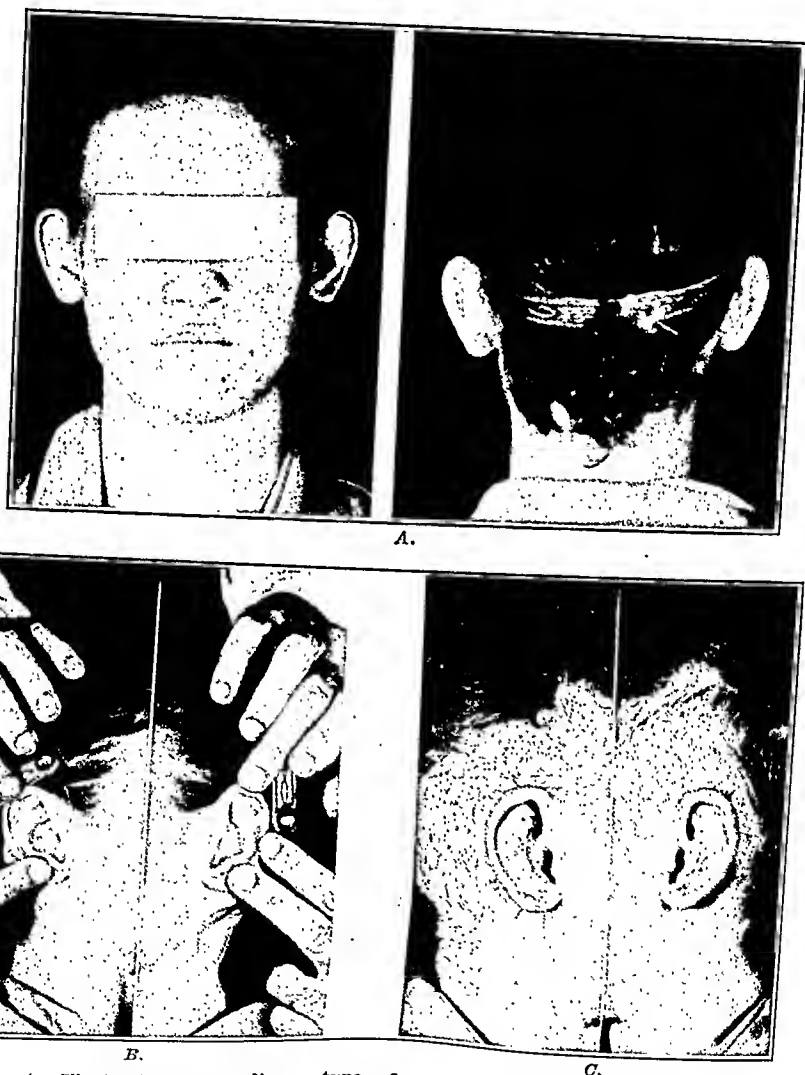


Fig. 4.—Illustrating the ordinary type of congenital bilateral prominent ears, seventeen-year-old girl. Marked mental distress. *A*, The buttressing folds of the antihelix are undeveloped and the erura are unfurled on each ear. *B*, With the ear reconstructed. *C*, Twelve days after reconstruction of the antihelices. The ridges to be marks stained by the brilliant green are still present in the skin, and the ends of the horsehair sutures can be seen projecting beyond the ear margins. *D*, Two weeks after operation. Note the difference in the position of the ears following the reconstruction of the antihelices. Since the ears were restored to normal position, the mental attitude of the patient has been vastly improved.

Prominent ears are fairly common. The reason that the cartilage does not fold into the normal, buttressing ridges in these cases is not

skin with subsequent closure to more complicated procedures in which the cartilaginous framework of the ear is involved. Excision of skin alone should be considered only in cases of slight deformity in young children, or where the cartilage is very soft, and even in these cases the ultimate result is uncertain. If we expect to get a lasting result, it is

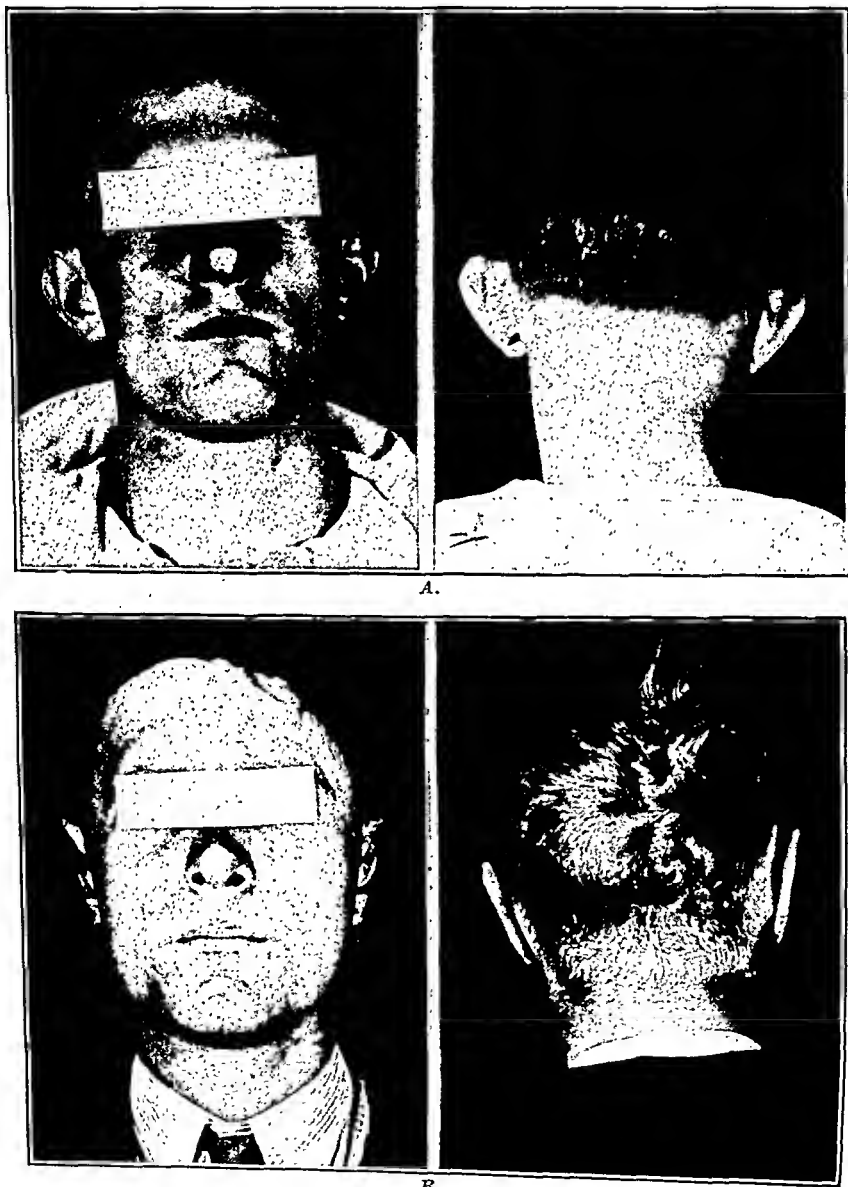


Fig. 6.—Illustrating congenital bilateral prominence of ears associated with un-curved helix, twenty-four-year-old male. Odd appearance interfered with obtaining suitable employment. *A*, Note the prominence and position of the ears. The crura of the anthelices are undeveloped as is the curl of each helix. The deformity in the right ear differs from that of the left ear. *B*, Result of reconstruction two weeks after operation. Nothing was done to the helix.

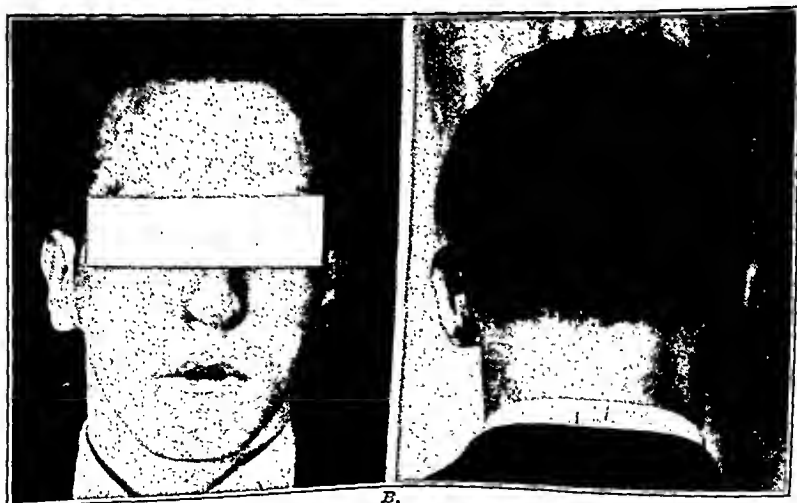
sequently correction of the macrotia is unnecessary. It is seldom that prominent ears are smaller than normal.

In congenitally prominent ears, we find that the cartilage of the ear is sometimes soft and floppy. Ordinarily, however, the cartilage has normal rigidity.

There have been a number of operations suggested for the correction of prominent ears. These vary from the simple excision of an ellipse of



A.



B.

Fig. 5.—Illustrating a moderate grade of congenital bilateral prominence of ears, nineteen-year-old male. Marked mental distress. Complaints of inability to get a job. A, The antihelices are incompletely developed. Note the position of the ears. B, Result after seven years. The ears are not quite as close to the head as they were immediately after the overcorrection operation, but there has been no change in position after the first few months. The mental disturbance caused by the prominence of the ears cleared up soon after operation.

not attempt at this time to review the various methods used. The purpose of this paper is to describe a technique which we have gradually developed, particularly for those deformities caused by abnormalities of the antihelix, and which we have been using for a number of years with satisfaction.

The method presents several points which have been very useful to us and while they may have been used elsewhere, as far as we can ascertain, they have not been reported in quite the same way that we use them.



Fig. 8.—Illustrating a marked case of congenital bilateral prominence of the ears. A, There is complete undevelopment of the supporting ridges of the antihelices. The ears stand away from the head almost at right angles. B, Three and one-half months after the restoration of the ears to normal position by reforming the antihelices. This patient was seen recently, seven years later, and the ears have stayed in good position. The mental distress ceased immediately after the patient observed his ears at time of first dressing.

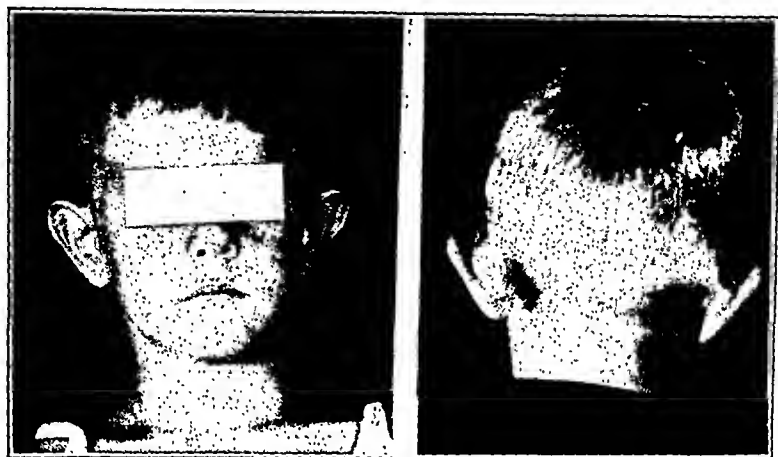
#### METHOD

We prefer a general anesthetic, usually avertin, 60 to 75 mg. per kilogram, supplemented by nitrous oxide and oxygen. The operation

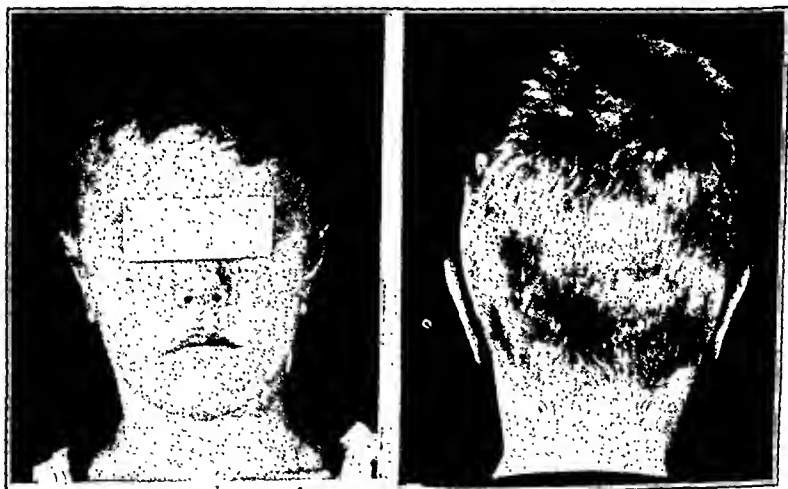


necessary to break the spring of the cartilage by some means, whether it is firm or soft, and to reconstruct the buttressing ridges so that the ear will be supported and will remain in the approximate position in which it is placed by the operation.

In order to overcome the resistance or spring of the cartilage, several procedures have been used: thinning the cartilage along the line of fold-



A.



B.

Fig. 7.—Illustrating congenital bilateral prominence of the ears, eight-year-old boy. Constantly in trouble on account of remarks made in school by his companions. *A*, Note the unfolded crura of the antihelices. The upper portion of the ears stands away from the head considerably further than the lower. *B*, Two weeks after the reconstruction of the antihelices. The ears appear somewhat too close to the head, but the retroauricular angle on each side is deep, and the ears will gradually come out slightly.

ing; incising the cartilage along this line; excising long narrow crescentic- or elliptical-shaped pieces of the cartilage along the line which is to be turned in; or both excising and incising the cartilage. We will

with cotton wet with alcohol; and this is followed by a thorough clean-up with ether, alcohol, and kalmarid.

The ear is now held in normal position against the side of the head, and its upper and posterior limits are marked on the scalp with 5 per cent brilliant green in alcohol in order to indicate the general position to be attained by operation. When the ear is in this position, it will be found that the portion of the antihelix which is unfolded will reform itself sufficiently to give the line of required reconstruction, and this line is marked out on the anterior surface of the ear with the brilliant green solution. Then along the full length of this line a series of punctures, five or six or more in number, and about 1 cm. apart are made in the following manner. An hypodermic needle, at least one inch

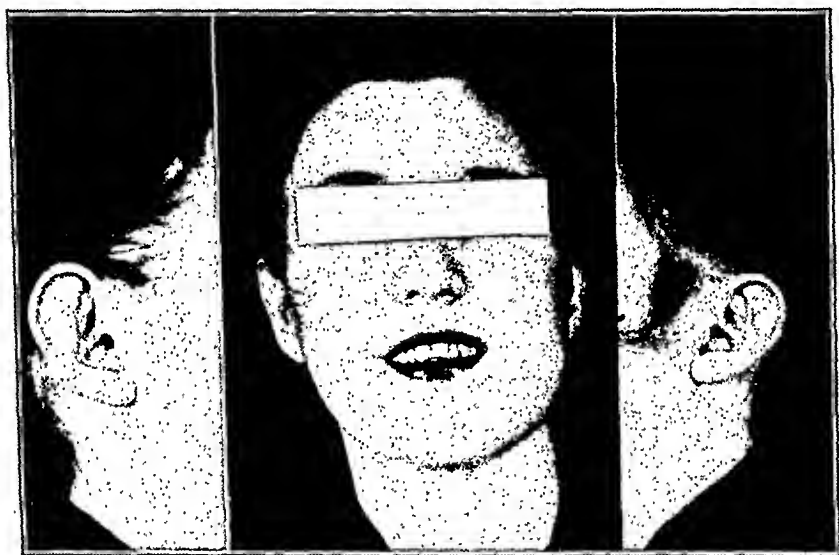


Fig. 9C.—See opposite page for legend.

long and about 24-gauge, dipped in brilliant green solution and placed at right angles to the anterior skin surface is thrust completely through the ear from front to back, coming out at a corresponding skin point on the posterior surface. When the needle emerges through the skin of the back of the ear, its point is touched with a toothpick swab dipped in the same solution, before it is drawn back again, and in this way sufficient dye is carried through the tissues to make the required marks on the cartilage but not enough to overstain, as would be the case if there were dye in the needle or syringe. A green puncture mark shows on the skin of the anterior surface of the ear where the needles enter and similar marks are found on the skin of the posterior surface of the ear where the needles emerge. The ear is drawn forward, the puncture marks on the back of the ear are connected by a line of brilliant green applied with a toothpick, and this line while damp is pressed against the skin of

can easily be done under local anesthesia, but it is tedious and we have found that the patient, in the long run, is better off under a general anesthetic. The patient is placed on a brain table with the face down. In this way both ears are fully exposed at the same time in the most



A.



B.

Fig. 9.—Illustrating congenital bilateral prominence of the ears, fourteen-year-old girl. Inferiority complex. *A.* Note the marked deformity and the lack of development, especially of the crura. *B.* Result three months after reconstruction of the antihelices. Note the newly formed supporting ridges and the position of the ears. The inferiority complex has been forgotten. *C.* Result after three and one-half years. Note the normal position of the ears and the permanence of the reconstructed ridges.

favorable operative position, and the clean-up and drape on both sides can be done before the operation is begun. The hair is shaved around the ear for a sufficient distance; the external auditory canal is plugged

sponge every portion of the anterior part of the ear is carefully and snugly packed, eliminating all dead space and giving absolute support to the readjusted cartilage. After the ear has been completely filled with the sponge bits, a single larger piece of seasponge is placed over the whole and secured by strips of adhesive. Over this is placed a snug bandage, care being taken to avoid pressure sloughs. Unless some untoward symptom presents, the dressing is allowed to remain undisturbed for ten days, at which time the horsehair stitches are removed, and a snug dressing is applied. All dressings are completely removed in another week, and the patient is instructed to hold the ears close to the head at night for about three months by a closely fitting bandage or skull cap.

#### COMMENTS

In our experience, we have never seen any of the maneuvers practiced by anxious mothers in trying to train prominent ears back into normal position accomplish the desired result.

Except in the mildest cases, excision of the skin alone with closure will not be permanently effective, since the spring of the cartilaginous framework of the ear is so continuously persistent that in time it will overcome any soft part closure; the scar and adjacent tissues will stretch and the deformity will recur. In order to obtain a permanent result, it is essential to break the spring of the cartilage of the ear.

By the removal of long elliptical or crescentic strips of cartilage with turning in of the edges or by properly placed incisions through the cartilage, the antihelix and other supporting cartilage ridges can be reconstructed. In some cases, it is necessary to excise more than one piece of cartilage or to break the spring of the cartilage in more than one place according to the degree and location of the deformity.

It is not possible to give specific directions as to exact amount of cartilage and skin to be removed, since each case varies and each ear in each case presents a different problem which must be solved individually.

Care must be taken to replace the two ears fairly symmetrically. If the denudation of skin behind the ear is too wide, we will find the retroauricular angle almost obliterated. The ears should not be made to adhere too closely to the skull, since an ear plastered permanently against the skull is almost as objectionable as one that is too prominent.

When an ear is abnormally large, in addition to being unduly prominent, the appropriate plastic operation which will reduce the size as much as is desired should be done, in addition to restoring the ear to its normal position.

After removal of portions of cartilage and reconstruction of the antihelix, the skin on the anterior surface may occasionally be thrown up into an abnormally prominent fold. This fold will often smooth itself

the scalp with the ear in normal position. This gives a slight greenish mark which is supplemented to make it more distinct, and the area inside these lines, which when the ends are extended and joined is more or less elliptical in shape, will be the skin area to be excised.

The excision is made, all bleeding is checked and necessary vessels tied. When the cartilage is exposed, a line of puncture points stained green can be seen in the cartilage itself which definitely marks out the direction and curve to be followed. Then, depending on whether an elongated crescent or ellipse of cartilage is to be removed or whether a simple incision through the cartilage is to be made, or whether both incision and excision are used, the selected procedure is carried out with a small sharp blade. We find that the finger in the anterior surface of the ear will give one a guide and will aid in preventing the perforation of the skin on this surface. If an area of cartilage is to be excised, the incision is made all around it and completely through it, and it is then stripped out with a thin flat elevator.

It is important to see that the incision or excision of the cartilage extends the full length of the antihelix and that all cartilage spring is divided so that there will be no resistance or tension when the margins are turned in to form the new antihelix. The new antihelix is formed by turning forward the margins of the cartilage to form a supporting ridge. This is done by passing a catgut suture (No. 0 or No. 1, plain) through the perichondrium on one side beginning about 0.5 cm. from the cartilage margin and coming out close to the margin. The needle is then carried across the defect and enters the perichondrium a similar distance from the margin and then out about 0.5 cm. from the defect. This suture is of the Lembert type. Four or five of these sutures are placed and then all are drawn up at one time and are tied in order. It will be found that the cartilage edges have been turned forward toward the anterior surface of the ear, replacing the unfolded portion of the antihelix, and that the ear immediately assumes a position which approximates normal. The skin is then closed with on-end mattress sutures of horsehair.

After the operation is completed, the ears will sometimes appear to be almost too close to the head, but in time the sharp overcorrection of the reconstructed antihelix will relax.

#### DRESSINGS

The dressing of the reconstructed ear is of considerable importance, since immobilization and perfect support of the newly adjusted cartilage are essential for a good result. The sutured line is painted with one-third strength tincture of iodine. A single layer of gauze impregnated with 3 per cent xeroform ointment is laid over the stitch line. Over this is placed a narrow strip of sterile seasponge between the ear and the scalp, and the ear is held close to the head. Then with small bits of sea-

# A HISTOLOGIC STUDY OF THE INTESTINE PROXIMAL TO CARCINOMA OF THE RIGHT SIDE OF THE COLON, ASSOCIATED WITH ANEMIA

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IT SEEMS to be generally believed that severe anemia associated with carcinoma of the cecum and the right half of the colon is due to some mechanism other than loss of blood from the ulcerated tumor.<sup>3, 5</sup> This impression has been general and often may be applied to distinguish clinically the symptoms of lesions in the cecum and ascending segment of the colon from those produced by lesions in the distal portions of the large intestine. That is, in carcinoma of the cecum the associated anemia may be severe and occasionally the only symptom. The anemia present in carcinoma of the right half of the colon is usually of the hypochromic type, which may be attributable to hemorrhage. However, cases are occasionally observed in which there is a macrocytic type of anemia similar to pernicious anemia. The blood findings do not therefore seem to have any direct relation to the presence or the absence of macroscopic blood in the feces. These circumstances form the basis for the opinion that carcinoma of the right half of the colon may exert a special influence on the blood findings in this disease.

Recent work, which was concerned with the relation of the gastrointestinal tract to the formation of blood, has demonstrated certain possible relations between the anemia and the physiologic disturbances produced by the lesions in the intestine. These physiologic disturbances may result from a number of pathologic conditions of the bowel;<sup>2, 4, 7</sup> in these conditions it has been suspected that anemia resulted from failure of the intestine to absorb iron and the hematopoietic principle. That is, there may be direct loss of hematopoietic substance or iron, such as could occur in the case of multiple intestinal anastomosis, diarrhea, and fistula. There also may be an alteration in the intestinal mucosa which results in malabsorption of antianemic substances; into this category should fall those benign and malignant lesions of the bowel which are associated with rapid elimination of intestinal contents.

The question of etiology of the anemias in intestinal diseases without gross hemorrhage has been approached experimentally by Seyderhelm, Lehmann, and Wichels.<sup>6</sup> They studied the blood of dogs which had intestinal strictures. Of ten dogs that had satisfactory intestinal stric-

down in time, but if it persists it can be reduced in size without difficulty at a secondary operation. One ear may be replaced at a time, but our preference is to operate on both under the same anesthesia.

The brilliant green puncture marks in the skin of the ear disappear within a few days and are frequently gone by the time the final dressings are removed. Unless something is done for these patients to correct the deformity, frequently we find that there is serious interference with complete mental and physical development.

Ordinarily we do not operate on children with abnormally prominent ears until they are four or five years old. We have operated on adults as old as forty-five years of age. As far as we can ascertain from observation of cases operated on when they were children, the operation described causes no interference with the normal growth of the ear.

#### SUMMARY

The use of the brain table in allowing exposure and comparison of both ears at the same time in the desired position is advantageous. The object of the procedure is to reconstruct the undeveloped or unfolded portion of the antihelix so that a rigid buttressing ridge, or ridges, will be formed which will support the ear in its normal position.

Perforating the tissues with the needle dipped in brilliant green solution in marking out the line of cartilage to be incised, or excised, is a distinct advance in technique. The importance of completely breaking the cartilage spring by incision or excision is emphasized, as we have never seen a permanent result unless the spring of the cartilage was broken.

In the method described, the sutures used in turning forward the cartilage edges to form the antihelix are all placed in the perichondrium, as the cartilage itself is friable, and none are placed in the periosteum of the skull.

The use of the seasponge as a postoperative dressing has been very helpful in fixing the reconstructed ridges and in immobilizing the entire ear.

After successfully restoring prominent ears to normal position, the appearance of the patient is vastly improved; the mental aspect is entirely changed for the better; and many adults are able to obtain suitable employment from which they had been barred on account of their bizarre appearance.

We have been able to follow some of our patients for years and have found that the procedure we have outlined is simple and satisfactory and that the results are permanent. So looking at the deformity both from the psychological and the practical standpoints, we feel that the restoration of prominent ears to normal position is without doubt justified and advisable.

regions above the lesions. Histologic examination of the ileum showed that the intestinal epithelium was not altered; the villi were normal and submucosa did not show any change. In none of the specimens examined were there changes in the intestinal wall which might suggest the possibility of alteration in the functional activity of the bowel.

#### COMMENT

It is important to know that the segments of the terminal portion of the ileum which have been studied showed no important changes in structure, although the patients had moderately severe anemia. There was no evidence of atrophy of the mucosa nor were there infiltrative changes in the bowel wall. The possibility of an absorption defect for antianemic substances in this condition seems to us less likely in explaining the anemia than the probability of loss of blood as a result of hemorrhage from the neoplasm. Basing their explanation on rational circumstantial evidence, Alvarez and his associates<sup>1</sup> have accounted for these anemias on the basis of bleeding. Carcinomas of the right half of the colon are usually larger and of longer duration than are those in other portions of the large intestine. About 15 per cent of carcinomas of the right half of the colon are symptomless, except for anemia which develops slowly. These patients may suffer a slow but constant bleeding, which is not macroscopically detectable in the feces.

Whatever the cause of anemia in cases of carcinoma of the right half of the colon may be, we do not believe it is due to objective structural changes proximal to the lesion in the colon or in the terminal portion of the ileum.

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tures, a macrocytic type of anemia occurred in two. In these dogs there was marked infection of the bowel above the site of the stricture. These authors therefore attached considerable importance to structural alterations caused by infection in the intestine proximal to the disease accounting for the anemia. The object of this work is to investigate the relation of such experimental findings to the explanation of the anemias which occur in carcinoma of the right colon of man. That is, an attempt was made to determine whether or not there were changes in the anatomic structure as the result of infection or other disease in the intestine proximal to carcinoma of the right half of the colon. Carcinoma of the cecum and ascending colon does not commonly result in marked obstruction unless intussusception occurs, but it may offer some barrier to the fecal current for a relatively long time and is situated at a strategic point for exerting influence on the small intestine.

We used surgical specimens which are most desirable for study since they are fixed immediately after removal and are free from changes in the intestinal mucosa which might be found in postmortem specimens. Ten cases of carcinoma of the right half of the colon, which was associated with anemia of varying severity, were studied. A description of these lesions and certain clinical data relative to the blood are recorded in Table I. Microscopic studies were made of the walls of the large intestine proximal and distal to the growths. Similar studies were also made of the ileum near the region of the ileocecal valve and at variable distances proximal to this region, depending on the amount of ileum removed at operation. Sections were stained with hematoxylin and eosin.

TABLE I

SITE OF THE LESIONS AND BLOOD FINDINGS IN CARCINOMA OF THE RIGHT SIDE OF THE COLON

CASE	SITUATION OF CARCINOMA	ERYTHROCYTES (PER CU. MM. OF BLOOD)	HEMOGLOBIN (GM. PER 100 C.C. OF BLOOD)
1	Ascending colon	4,090,000	10.7
2	Cecum and ascending colon	4,340,000	9.5
3	Cecum and ileocecal region	4,320,000	7.3
4	Hepatic flexure	3,290,000	10.7
5	Ascending colon	4,140,000	10.1
6	Ascending colon	3,800,000	8.5
7	Ascending colon	3,450,000	9.5
8	Ascending colon	3,970,000	8.5
9	Ascending colon	2,600,000	7.0
10	Hepatic flexure	4,140,000	11.7

No significant and constant changes were observed in the mucosa, submucosa, or muscular coats of the large intestine. The colon proximal to the growth was not different from that distal to the growth. Infiltration with lymphocytes and polymorphonuclear leucocytes was not prominent and never marked in the sections of the bowel taken from

extensive incisions through large muscles, such as are to be found on the posterior aspect of the thorax, invite considerable blood loss and are potentially shock producing every surgeon of experience knows. Gatch and Little have determined the amount of blood loss in operations of various kinds and have indicated that incisions through large muscles are usually attended by greater loss of blood than those practiced in meticulous hemostasis would anticipate.

Alexander has sketched the early history of thoracoplasty and has summarized the views concerning the technique of its performance which serve as the basis for the modern operation.\* The general plan of procedure in extensive chronic empyema is essentially the same, longer segments of the lower ribs, however, being excised and sacrifice of the thickened parietal pleura often being mandatory to obliterate the empyema cavity.

#### THE AUTHOR'S OPERATION OF RIB REMOVAL

Every surgeon who strips a rib from its periosteal bed, preparatory to its removal, takes advantage of the direction of insertion of the external intercostal muscle bundles upon the rib. On the upper side, he begins behind and strips in a forward direction with an appropriate instrument; on the lower margin this rib is freed by stripping in the opposite direction. Some years ago, it occurred to the writer that preliminary excisions of the anterior costal cartilages and division of the upper three ribs would facilitate performance of the upper thoracoplasty. My associate, Herbert A. Carlson, made a preliminary report upon this method in 1934 and together with W. F. Bowers we have reported recently a more extended trial with the procedure.

The removal of ribs through short anterior and posterior incisions would appear to be a natural sequel to that method of rib excision. The writer has had occasion to prove to his own satisfaction that the entire rib can be removed in this manner. First, the rib is divided anteriorly either at the sternum or at the chondrocostal junction and the intercostal muscle bundles are separated along the lower margin of the rib. At a second posterior operation, the rib is divided at the site of articulation with the transverse process, the intercostal muscle bundles are separated from the superior border of the rib, and the rib is then pulled out through the tunnel of the posterior incision. In both the anterior and the posterior operation, the surgeon stands on the contralateral side.

#### TECHNIQUE

*The Anterior Operation.*—The patient lies flat upon his back on the operating table. When the costal cartilage and anterior end of the first rib are to be excised, a routine procedure in thoracoplasty for tuberculo-

\*In Alexander's new book *The Collapse Therapy of Pulmonary Tuberculosis*, which has appeared since this paper was written, there is an excellent summary of various manners of doing the anterior operations.

## COMPLETE COSTECTOMY

### A NEW AND SIMPLE METHOD OF RIB EXCISION APPLICABLE IN THORACOPLASTY AND CHRONIC EMPYEMA\*

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THE gain for the patient and the risk assumed are the chief considerations in deciding upon the advisability of an operation of election. The risk of an operative procedure is difficult to gauge in a given instance. No experienced surgeon essays to do it with absolute accuracy. Unpredictable findings and occurrences in an operation still attach something of the uncertainty of prophecy to the estimate of the surgical risk. Apart from the risks peculiar to operations upon certain tissues or organs, the principal concern relates to the formidableness of the procedure and the physical status of the patient. Not uncommonly, patients whose ability to withstand surgical intervention is poor need operations of the greatest magnitude. No wonder that the surgeon's responsibility is great and that he occasionally shortens life when he proposes to lengthen it or make it happier.

Thoracoplasties for tuberculosis or extensive chronic empyema as currently performed are formidable operative procedures; and the patient, who with the aid of his surgeon's counsel must weigh the gain and risk involved, is often in poor physical condition. The innovation of alternative remedial measures or operations of lesser magnitude which will accomplish the same end are urgently needed in order that the hazard may be lessened and the benefits of such therapeutic agencies be made available to a larger group of despairing patients.

The operation of thoracoplasty for pulmonary tuberculosis consists of a series of one to four or more operations in which the paravertebral portions of the ribs are exposed through long incisions. Because of the difficulty of exposure, the incision for the removal of the upper ribs is of necessity greater in length than the segments of rib removed. The general plan of complete or subtotal removal of the upper three ribs with excision of lesser lengths of succeeding ribs in multiple stages is now the generally accepted plan of operation. The present trend has been toward a more adequate collapse of the upper lung by more extensive removal of the first to sixth or eighth ribs preserving the lower bony thorax intact.

The general principle of an incision approximately as long as the rib to be removed is described in all texts upon thoracic surgery. That

\*Aided by a grant from the research funds of the Graduate School.  
Received for publication, Sept. 5, 1937.

sis, the arm is extended and abducted upon an arm-board to alter the direction of the subclavian vessels and elevate them from their normal course over the first rib. A short transverse skin incision about five to eight centimeters in length affords ready access (Fig. 1a). The fibers of the pectoralis major muscle are separated; the periosteum is incised, and a periosteal separator of the O'Brien type is inserted between the lower margin of the rib and its periosteal bed; with surprising ease, this instrument can be pushed along the edge of the rib as far as its angle posteriorly (Fig. 1). If care is observed in its withdrawal, the hook

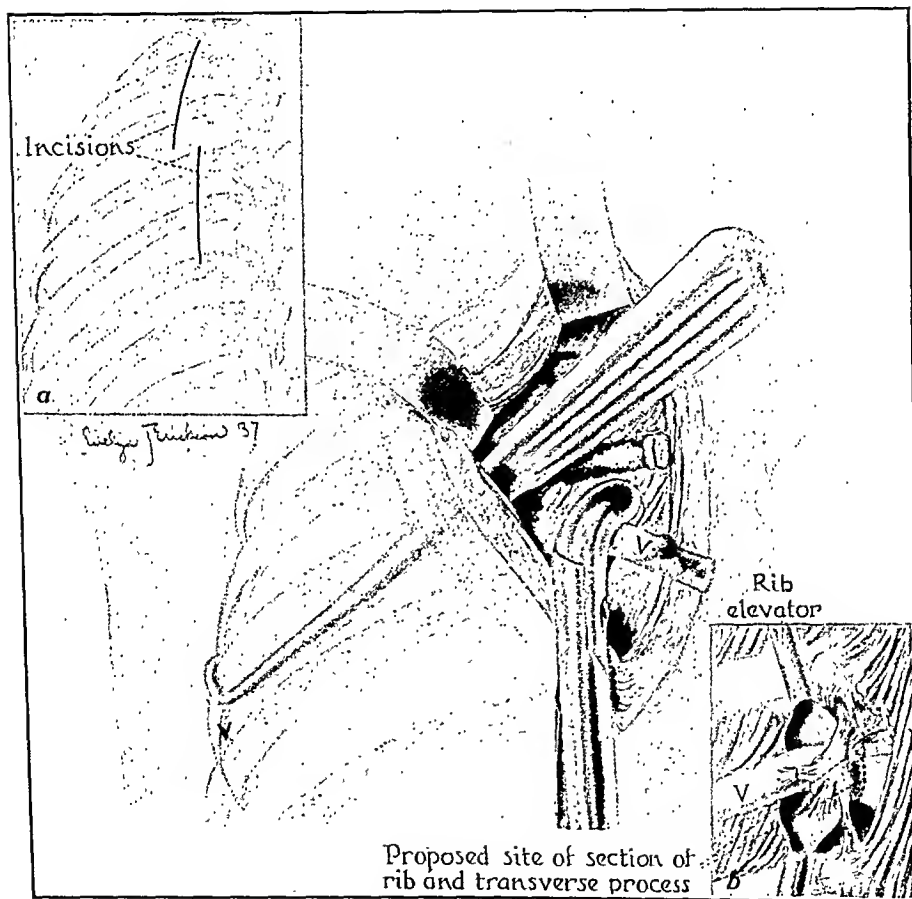


Fig. 2.—The posterior operation in which the ribs are removed. The stripper is being pushed in a forward direction along the superior border of the rib. After exposure of the rib through the incision as shown in Fig. 2a, the costotransverse articulation is exposed (Fig. 2b) by cutting and separating the short and long levator muscles of the rib as well as the multifidus and intertransverse muscles and the intertransverse and costotransverse ligaments. After all the ribs to be removed have been sectioned, the rib is rotated into the wound and its separation from its periosteal bed proceeds as shown. By gentle pushing with a small sponge on a long curved hemostat, the residual attachment of internal intercostal muscle fibers (see Fig. 1 and legend) and that of such accessory muscles as the pectoralis minor or serratus anterior can be dealt with quite easily (see text). Elevation of the muscles of the chest wall on a retractor in the intercostal space is a valuable expedient which facilitates this procedure.

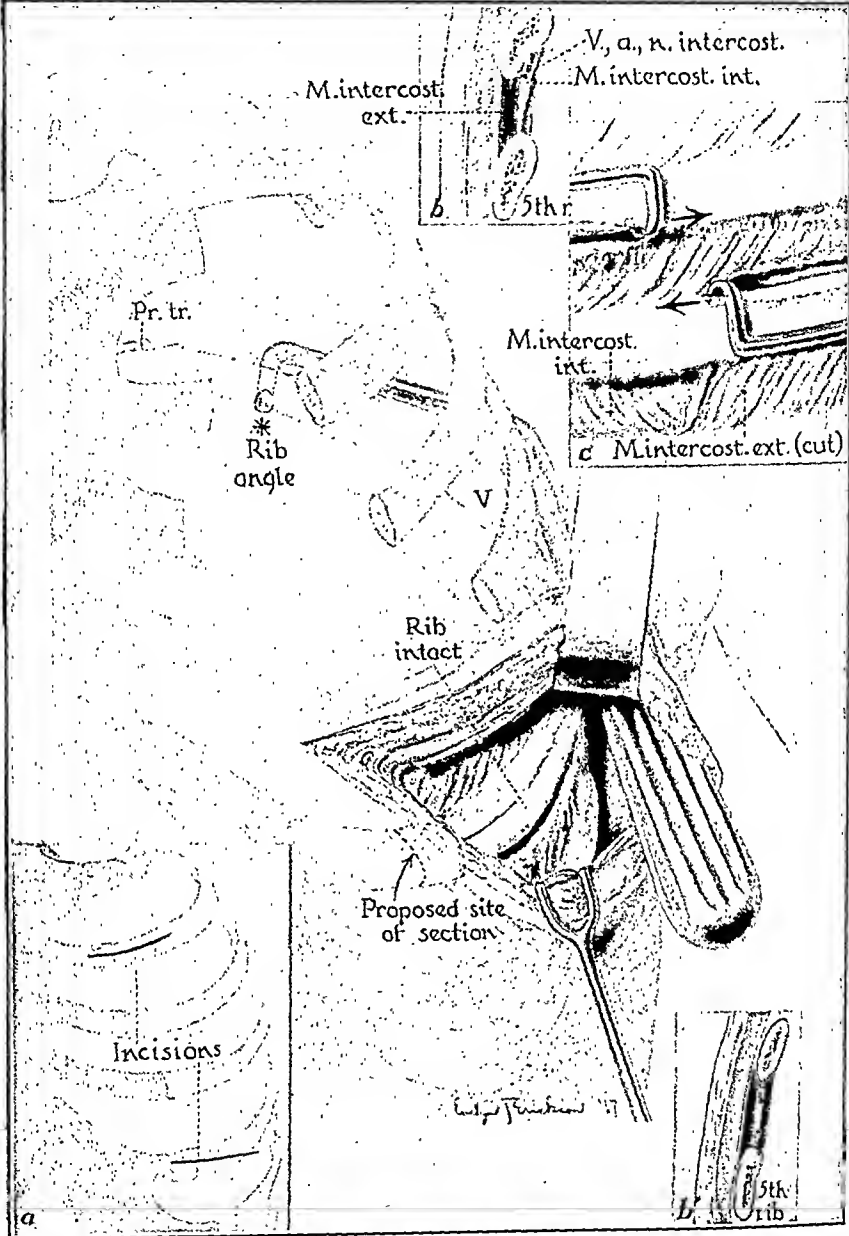


Fig. 1.—The first stage of complete costectomy—the anterior operation. The periosteal stripper is being pushed along the lower margin of the fifth rib. It has not yet been sectioned anteriorly. The extent of bone and cartilage removal (extrapleural thoracoplasty for tuberculosis) of the first to fourth ribs is shown. The stripper can be pushed as far as the angle of the rib posteriorly. The muscles of the lateral thoracic wall are elevated on a retractor in the interspace as the periosteotome is pushed along the lower edge of the rib. *a*, The anterior incisions (see text). *b*, The nature of attachment of the external and internal intercostal muscle fibers to the ribs in the vicinity of the angle of the rib; on the upper rib, shown in this insert, it is apparent that the periosteal stripper pushed posteriorly along the lower margin of the rib will detach only the fibers of the external intercostal muscles. On the lower rib, however, it is evident that the stripper will detach both internal and external intercostal muscle bundles (see text). *b'*, The nature of attachment of external and internal intercostal muscle fibers to the rib ventral to the axillary line. It is apparent that the periosteal stripper will separate both muscles from the rib when pushed along the borders of the rib. *c*, The direction of insertion of the external intercostal muscle bundles accounts for the simplicity of this method of rib removal. The internal intercostal muscle fibers, it is to be observed, run in the reverse direction. The external intercostal muscle bundles are deficient anteriorly between the costal cartilages; the internal intercostal muscle bundles are missing posteriorly, proximal to the angle of the rib.

the distal half of the transverse process are well exposed (Fig. 2*b*). Periosteal separators of the Hedblom type are then placed beneath the rib and transverse process and both are cut through with a large costotome (Horsley laminectomy or Bethune rib shears). When the ribs to be removed have all been cut, each in turn is seized with a lion-jaw forceps. The scapula is not seen during any stage of the posterior operation and there is no necessity to retract it. The rib is elevated and rotated into the wound. Forceful elevation of the muscles of the chest wall upon a retractor with a long but narrow blade inserted in the interspace overlying the rib to be removed is an important item in the technique, as it is in the anterior operation. A periosteal separator of the O'Brien type is now pushed along the upper margin of the rib, freeing it from the external and internal intercostal muscle bundles. The fibers of the external intercostal muscle bundle proximal to the angle of the rib on its lower margin are separated by pulling the periosteotome posteriorly. The periosteal separator is then pushed forward along the lower margin of the rib and apart from the attachment of some of the fibers of the internal intercostal muscle bundle and those of such muscles as the pectoralis minor or serratus anterior, the rib is wholly free. By plying the periosteal separator alternately along the outer and inner surfaces as well as along the upper and lower margins over the entire length of the rib, aided by gentle pushes with a sponge mounted on a long forceps, the whole rib is usually removed with ease. When the anterior scalene muscle has been detached from the scalene tubercle at the anterior operation, the first rib can also be removed in this same manner. The wound is closed with a few sutures of buried silk. In pushing the attached muscle fibers off the rib with a sponge, there is occasionally some bleeding—probably from an intercostal vein. The wounds are invariably dry, however, when closed, and no drainage is employed; and without exception primary healing has been obtained in all thoracoplastic wounds (sixteen patients). More detailed observations will be narrated in a subsequent report.

Twice, a small rent has been made in the pleura (anterior operation) which occasioned no difficulty. I have satisfied myself by dissections on the fresh cadaver at postmortem examination that a rib can be stripped in either direction by this method in the presence of a normal pleura without tearing it. A small abnormal bony excrescence on the rib at the site of muscle insertion is the usual cause of this accident. With the help of Mr. John Phelan, of the Scientific Apparatus Shop of the Department of Physics at the University of Minnesota, I hope to develop improved instruments which will facilitate this procedure. In general, the O'Brien rib stripper is quite satisfactory for the anterior operation. The hook is probably somewhat longer than it need be and the shank should be a little longer. It is interesting to speculate on the development of an instrument which will strip the rib, then cut it and

will not engage in the tissues of the chest wall. The rib is then sectioned anteriorly at the point selected for its division, and the overlying muscles of the chest wall are elevated on a Deaver type of retractor with a long but narrow blade. The rib is now seized and elevated with a lion-jaw forceps. With a gentle push of a sponge upon a curved hysterectomy clamp, any fibers of the external intercostal muscle still attached to the lower margin of the rib are readily separated. About 3 to 5 cm. of the anterior end of the rib is then excised. By sliding the incision up or down with appropriate retraction, three or four ribs can be dealt with in the manner here described. Bleeding is minimal. A few ligatures of fine silk suffice for secure hemostasis and the separated fibers of the pectoralis major muscle are approximated by a few interrupted sutures. An external compression bandage as described elsewhere<sup>7</sup> is applied.

The reaction following this procedure is usually slight and in from seven to ten days the ribs can be divided posteriorly and removed. In the anterior operation for tuberculosis, I have removed regularly the costal cartilages of the upper three ribs and since May of this year, when the operation here described was first done, on several occasions I have removed the cartilages from the upper seven ribs. The degree of collapse obtained by this type of procedure has been very satisfactory. Bone not cartilage regenerates from the perichondrium and an infirm anterior chest wall has not been observed following excision of the costal cartilages. Roentgen films following thoracoplasty employing this method of operation suggest that an earlier and more liberal calcification occurs along the periosteal beds than with the usual thoracoplastic procedure.

#### THE POSTERIOR OPERATION

In the excision of the upper ribs which lie beneath the scapula, the patient is placed prone on the operating table with the neck flexed and the face engaged in the type of head rest employed for operations upon the cerebellum. The lucid drawings made for me by Miss Evelyn T. Erickson, of the Department of Medical Art of the University of Minnesota, illustrate well the technical details of both the anterior and the posterior operations.

An oblique incision indicated in Fig. 2a, as employed by White, Smithwick, Allen and Mixer, is probably to be preferred in the excision of the upper three ribs. The fibers of the trapezius and both rhomboid muscles are split and those of the erector spinal group (iliocostalis and longissimus) are separated and with appropriate retraction direct access is obtained upon the neck of the rib and the transverse processes of the vertebrae. The intertransverse muscles and ligaments and the multifidus muscles and posterior costotransverse ligaments overlying the costotransverse articulations are snipped with scissors and separated with a suitable dissector until the neck of the rib and

my thought that the regenerated rib could be left on the parietal pleura and a satisfactory obliteration of the cavity would be obtained. At the second operation, however, the posterior thoracic wall was found to be so rigid that it was necessary to excise a segment of the parietal pleura to effectually obliterate the cavity, a pedicled muscle slip being simultaneously sutured over the bronchial stoma.\*

In the small chronic empyema where the excision of short segments of two to three ribs will satisfactorily obliterate the residual cavity, the plan of operation suggested here will have no place. In the chronic empyema cavity of intermediate size, which has had no previous thoracoplastic repair, the excision of the overlying ribs by the method here described would appear to be a valuable procedure in that the parietal pleura need not be sacrificed. Some time ago,<sup>6</sup> I reported upon a plan of saving the parietal pleura by a process of ribboning in order to prevent the occurrence of abdominal hernia in operations for extensive chronic empyema cavities. The plan of operation described here, however, is from many standpoints a great improvement over that procedure. The pleural space cavities persisting after total pneumonectomy, it would appear, could be obliterated simply and effectively by complete removal of the ribs overlying the cavity by this plan of operation.

#### REACTIONS ATTENDING THE OPERATION

The lesser operative reaction attending anterior chondrocostectomy preliminary to the performance of the usual posterior thoracoplastic operation has previously been discussed.<sup>7</sup> Rib excision with avoidance of long posterior incisions has also contributed materially to decreasing the operative as well as postoperative reaction. Dyspnea has not been observed in any of the patients with pulmonary tuberculosis for whom thoracoplasty has been done by this method. This occurrence suggests that extensive division of the muscles of the thoracic wall, as necessitated by the usual thoracoplastic operation, may be even a more important factor in the production of mediastinal flutter and dyspnea than is rib excision. Whether a more satisfactory collapse will be obtained by this than by the usual method of operation remains to be seen. Persistent elevation of the shoulder on the operated side—an unfortunate occurrence which not uncommonly attended upper thoracoplasty performed through a long incision, has not been observed to follow this plan of operation.

It is to be noted that in this procedure the cartilaginous junctions of the rib with the sternum anteriorly and with the transverse process posteriorly are destroyed. When the rib regenerates, these ordinary sites

\*This patient, whose cough had been very bothersome, had had frequent pulmonary hemorrhages for years with similar bleeding through the external fistulous tract. Gentle continuous suction was applied to the catheter in the empyema cavity before operation and through convalescence; cessation of cough was immediate and complete. The employment of this expedient in the repair of bronchial fistulas where drainage is great would appear to be distinctly worth while.



permit separation of the periosteum on the opposite side as the instrument is withdrawn. Whereas the construction of such an instrument for use in chronic empyema is entirely feasible, it does not appear likely that in the presence of a normal pleura its employment would be as safe as a two-stage procedure.

#### THE REMOVED RIBS

A few short strands of muscle fibers often remain attached to the removed ribs in the presence of a normal pleura (thoracoplasty for tuberculosis). I have previously<sup>6</sup> directed attention to the ease with which ribs may be separated from their periosteal beds in the presence of chronic empyema and suggested at the meeting of the American Thoracic Society in 1935 that long lengths of ribs could be removed by a process of tunneling in chronic empyema. As may be supposed, therefore, the very longest ribs can be excised in chronic empyema with this method, and the removed ribs often fail to exhibit traces of attached muscle fibers. Coincident with thickening of the parietal pleura in chronic suppuration of the pleural space, changes (enlargement) in the rib occur, in consequence of which the envelopment of the rib by the periosteal sheath becomes much looser.

#### THIS METHOD OF RIB REMOVAL IN CHRONIC EMPYEMA

Two total empyemas in which expansion of the lung could not be effected have been satisfactorily collapsed with rib removal alone without removal of thickened parietal pleura. One of them concerned a young woman in extremely poor physical status with a tuberculous empyema. The parietal pleura in areas was 2 cm. in thickness. Yet this large cavity was collapsed by four relatively simple operations. The second to the tenth ribs inclusive were divided anteriorly in two sittings through two transverse incisions. In two subsequent operations employing vertical incisions posteriorly (the lower first), the first through the eleventh ribs were divided and removed. The other patient was a young man with a total empyema and a fistula of the thoracic esophagus which occurred in consequence of pneumonia, pulmonary and mediastinal abscess, nine months previously. Save that a small fistulous tract, whose capacity is about 10 c.c., still leads to the esophageal fistula which is still open, the empyema cavity has been completely obliterated and without excision of parietal pleura.

Two near total empyemas have also been completely closed with a similar plan of operation. In another patient with a persistent chronic empyema with enduring bronchial fistula who had undergone three thoracoplastic operations for its obliteration elsewhere twenty years ago, I found that this plan of operation was not suitable. I divided the rib anteriorly (second through tenth in one operation) and removed segments up to the regenerated rib, later doing the same posteriorly. It was

without the excision of parietal pleura. The technique of the method owes its simplicity to freeing the rib in the direction of insertion of the external intercostal muscle bundles.

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for movement of the rib become ossified and fixed. There would appear to be, therefore, an additional theoretical consideration in favor of complete osteotomy as the operative procedure of choice in thoracoplasty for tuberculosis. For in addition to collapsing the pulmonary cavities, complete osteotomy fixes the chest wall so that the normal motion of the ribs in respiration is lost. The external intercostal muscles (muscles of inspiration) and the internal intercostal muscles (expiratory), to be certain, constitute strong muscle masses which collectively have an enormous power. Yet, when the sites of normal rib movement are destroyed, the to-and-fro motion of this portion of the chest wall in respiration must be minimal.

A condition somewhat disturbing to the surgeon in the acceptance of this plan of operation for thoracoplasty for tuberculosis may be the increased number of operations. However, the patient who does not elect the safest procedure is in my experience, unusual. In chronic empyema the second through the tenth ribs anteriorly have been divided on two occasions in one sitting with surprisingly little reaction. A short time later the fifth through the tenth and eleventh ribs were sectioned and removed posteriorly by this plan of operation in one sitting. In the presence of a thin pleura, as is to be found usually in tuberculosis, I have continued to be conservative with the extent of rib excision in the vertical direction, dividing only three ribs at each operation. In two instances (upper stage) four have been divided and later removed through the posterior incision without untoward effect. The operations can follow one another, however, in five to seven days (ten to fourteen intervening usually between the second and third operations) and the patients leave the hospital just as soon and in much better condition than after the more formidable usual thoracoplasty which taxes the patient's strength and endurance far more. The interval of time between the first and last operations is usually less than a month.

Whereas this plan of operation may extend somewhat the indications for the performance of thoracoplasty to the patient whose physical status is poor, I would utter a word of warning concerning enlarging the indications of thoracoplasty for tuberculous lesions. The operation must not be done on patients with exudative tuberculosis but only when evidence of reactive proliferation and evidence of healing have become manifest.

#### SUMMARY

A new method of rib removal is described in which the whole rib, or whatever portion is deemed desirable, can be excised through short incisions. Extensive rib excision by this method is less formidable than the usual thoracoplastic operation. In the closure of large chronic empyema cavities, it is particularly valuable in that the cavity may be completely obliterated by relatively simple operative procedures and

pigs against colon bacilli infections by previous intraperitoneal injection of small amounts of sodium chloride. He described three clinical cases in which sterile salt solutions were injected prior to operation. Miyake (1904), working with von Mikulicz, used preparations of killed colon bacilli as well as materials previously used by Issaeff and Ivanoff. He described marked increases in the numbers of cells in the peritoneal transudates. Miyake protected rabbits from peritonitis of fecal contamination by inducing a hyperleucocytosis by injections of nucleic acid or killed cultures of colon bacilli. On the basis of Miyake's work, von Mikulicz (1904) used nucleic acid and sodium chloride in a large series of clinical cases. Aschner and von Graff in 1911, and von Graff in 1912, concluded, however, that no beneficial results were obtained from using the preparations of Miyake and von Mikulicz.

Following these earlier attempts to immunize the peritoneum, very little progress was made in this direction until the recent decade. Johnson (1927) recommended the use of amniotic fluid as a means of preventing peritonitis. Young and Marks (1934) used amniotic fluid in cases of colonic resection; they described a polymorphonuclear infiltration into the exudate of guinea pigs seven hours after the injection of 10 e.c. of the fluid. Herrmann in 1929 prepared a vaccine of killed streptococci and colon bacilli and protected a large number of rabbits from fecal peritonitis. He attributed this protection to some specific local peritoneal immunity. Morton (1929) protected rabbits against lethal doses of hemolytic streptococci, not only by intraperitoneal injections of streptococcal filtrates, but by injections of dextrose, glucose, and sodium chloride as well. Steinberg and Goldblatt (1927<sup>31</sup> and 1928<sup>10</sup>) reported the survival of a large number of dogs, immunized by injections of living and killed colon bacilli, after the intraperitoneal injection of fecal materials. No cellular data were included. Subsequently, in 1933,<sup>32</sup> they reported the cytologic response in the peritoneum of dogs to injections of colon bacilli suspended in tragacanth. Webb (1931) reported on the cellular response in the peritoneal spaces of white rats after the injection of albumin and of carbon particles. The reaction of the human peritoneum to the vaccine was reported by Barger and others<sup>2, 4, 13, 28, 33</sup> in 1933 and by Dixon and Rixford in 1934. Clinical results following the use of the vaccine were reported by Dixon and Barger in 1935. Johnson (1936),<sup>16, 17</sup> and Johnson, Coonse, Hazard, Foisce, and Aufranc (1936) reported their studies of the cytologic response in the peritoneum of dogs which had received intraperitoneal injections of amniotic fluid concentrate, colon vaccine, physiologic saline solution, and merthiolate in physiologic saline solution. The maximal cellular reaction occurred in twelve hours in animals that received amniotic fluid and at twenty-four hours in those that received the vaccine. Feagles and Bain in

## THE CYTOLOGIC RESPONSE OF THE PERITONEAL FLUID TO CERTAIN SUBSTANCES\*

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RECENT advances in the prevention of peritonitis by the preoperative injection of certain substances into the peritoneal space have stimulated considerable research in recent years on the cytologic reactions of the peritoneum to various stimulating agents. It has been established both clinically and experimentally that the introduction of certain substances into the peritoneum will incite the production of a defense exudate consisting of varying amounts of serum, leucocytes, fibrin, and other products, effecting thereby a defense reaction.

This cytologic and physicochemical reaction by the peritoneum to parenterally introduced agents is said to immunize it against infection. Two agents are now generally employed for this purpose: anti-peritonitis vaccine made from killed cultures of colon bacilli and streptococci (Rankin and Barger, 1929), and a purified concentrated bovine amniotic fluid from which the serum albumins and lipoids have been removed (Johnson, 1927). Immunization is induced by injecting either the vaccine or the amniotic fluid concentrate directly into the peritoneum thirty-six to forty-eight hours prior to surgical intervention. The cellular response to the irritant is believed to be at a maximum at this time, and some authors refer to the reaction as a hyperleucocytosis.

Stimulation of the peritoneum to produce an exudate in the body cavity and to produce immunologic reaction was first accomplished some forty years ago. Issaëff and Ivanoff in 1894 showed that they could protect animals from cholera by previously injecting various substances into the peritoneal space. They used water, urine, bouillon, serum, nucleic acid, and tuberculin, and thereby induced a hyperleucocytosis in the peritoneal exudate sufficient to protect against cholera. Durham, in 1897, protected rabbits against typhoid bacilli by previously injecting sodium chloride, and he recommended that prophylactic intraperitoneal injection of suitable sterile material be made twenty-four hours before opening the peritoneum when there was danger of contamination. Likewise Solieri (1902) protected guinea

\*The Wm. S. Merrell Company, of Cincinnati, Ohio, kindly furnished the sodium ricinoleate which was used in these experiments.

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Received for publication, April 12, 1937.

sodium ricinoleate in the peritoneal space of rabbits with the response induced by antiperitonitis vaccine.

#### METHODS

Only healthy adult white rats of the Wistar strain, weighing from 180 to 225 gm., were used in this study. Using the technique described by Montgomery (1932), a small capillary glass pipette was forced through the abdominal wall into the peritoneal space. The small amount of fluid which readily entered the pipette was placed on a clean slide and an adequate amount was drawn up into a leucocyte counting pipette for determining the total number of cells per cubic millimeter of fluid. The portion remaining on the slide was then stained with Wright's stain or with May-Grünwald-Giemsa stain for the differential count.

In order to determine the total number of cells present in the peritoneal space, it was necessary to know the amount of fluid exudate which was present. This was done by killing the animal by exsanguination, quickly opening the peritoneum, and carefully taking up on previously balanced filter paper all available free fluid. The increase in the weight of the paper was accepted as the weight of free fluid, and 1 gm. of exudate was considered the equivalent of 1 c.c. Knowing the number of cells per cubic millimeter, the number of cubic millimeters of fluid and the differential distribution, it was easy to compute not only the approximate number of cells in the peritoneal space, but also the number of histiocytes, lymphocytes, and eosinophilic, neutrophilic, and basophilic leucocytes as well. Twenty-three healthy male rats were used to assemble the control data with which the data derived from the rats receiving the vaccine, the amniotic fluid, and the sodium ricinoleate were contrasted (Table I).

Eighty rats were used to determine the cytologic response of the peritoneum to each of the three substances tested: namely, antiperitonitis vaccine, amniotic fluid, and 2 per cent sodium ricinoleate.

TABLE I  
CONTROL DATA ON PERITONEAL FLUID OF HEALTHY NORMAL RATS

AMOUNT OF PERITONEAL FLUID, MG. (23 RATS)	NUMBER OF PERITONEAL CELLS (100 RATS)		PERCENTAGE OF DISTRIBUTION OF LEUCOCYTES (100 RATS)
	PER CU. MM.	IN PERITONEUM	
223.0 ± 9.9	101,266 ± 3,391	22,582,318	Mononuclears: 79.77 ± 0.28 Eosinophiles: 14.75 ± 0.93 Basophiles: 5.25 ± 0.35 Neutrophils: 0.08 ± 0.02

Thus a total of 240 test rats were used in the study. Each animal received 1 c.c. of one of these substances intraperitoneally. Ten animals of each of the three groups were killed at 1, 3, 6, 12, 24, 48, 72, and 168 hours after injection.

1936 reported excellent clinical results from the use of a peptone broth in cases of peritonitis. No experimental data on the use of this broth have been assembled.

In most of the studies on the cellular distribution in peritoneal exudates which appear after intraperitoneal injections of the various substances, conclusions were based on the total number of cells per cubic millimeter and on the relative distribution of these cells. No attempts have been made to determine the quantitative distribution of cells occurring in the peritoneum in response to any of the immunizing agents.

This present report covers our study of the qualitative and the quantitative cytologic response of the peritoneum of white rats to antiperitonitis vaccine, to concentrated amniotic fluid, and to sodium ricinoleate. Sodium ricinoleate has been shown to detoxify large amounts of lethal toxins without destroying their antigenic power. When ricinoleate was added to 100 lethal doses of tetanus toxin, the material was rendered harmless, but its capacity to produce large amounts of protective antibodies was retained (Larson, Evans, and Nelson, 1924, 1925).

Sodium ricinoleate is a derivative of castor oil and, according to Rider<sup>26</sup> (1931), is composed largely of ricinoleic acid glyceride. Methods of purification have been described by Rider,<sup>27</sup> so that a chemically pure sodium ricinoleate is now available. It inactivates diphtheria toxins. It is highly hemolytic when given intravenously and causes some liquefaction necrosis when injected intramuscularly. Some irritation is induced when it is given intraperitoneally, but it is better tolerated by animals when given in this way. A review of the experimental and clinical use of the drug up to 1932 has been made by one of us (Seeley).

Rea and Wangensteen (1934) found sodium ricinoleate most effective in the prevention of intraperitoneal adhesions in rabbits. They also found that many of the histiocytes of the peritoneal exudate were either killed or injured by the drug, showing its destructive effect on living cells as well as on bacteria. Wangensteen in 1936<sup>34, 35</sup> reported the use of 1 per cent sodium ricinoleate on all mucous surfaces in cases of gastric resection for cancer, the purpose being to reduce the hazard of infection. Gillette (1936) reported the use of sodium ricinoleate in a series of 300 cases, and he found it of definite value in cases of advanced peritonitis; he believed it preferable to vaccines and amniotic fluid.

Johnson, Coonse, Hazard, Foisee, and Aufranc (1936), however, found sodium ricinoleate a distinct menace in the presence of postoperative infection. They found it extremely irritating and observed widespread cell destruction in the presence of the drug. Corwin, in 1936, working in this laboratory, has compared the cytologic response to

sodium ricinoleate in the peritoneal space of rabbits with the response induced by antiperitonitis vaccine.

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We determined for each rat at the time of killing the total amount of fluid present in the peritoneal space, the total number of cells present per cubic millimeter of fluid, the percentage distribution of the various cells comprising the exudate, and the total number of polymorphonuclear and mononuclear leucocytes in the peritoneum. The average of the ten determinations made for each item was accepted as representative of the conditions which existed at each period of observation throughout our study.

#### OBSERVATIONS

*Weight of Fluid Present in the Peritoneal Space.*—The average amount of fluid present in the peritoneal space of a healthy adult control male rat, according to our method of recovery, weighed 223 mg. (Table I). The data covering the weights of the fluid in each animal killed at each period during the study have been condensed in Table II. It is clear that the injection of either the amniotic fluid concentrate or the antiperitonitis vaccine caused some considerable increase in the amount of fluid exudate in the body cavity, but the amount in those animals which received the sodium ricinoleate was eight to ten times as large as in the control animals. Even at one hour after injection, the peak of the response to sodium ricinoleate had been reached when the volume of exudate recovered was over seventeen times the amount present before the injection was made. The fluid of those animals receiving the amniotic fluid and the vaccine was clear and colorless, but that of those receiving the ricinoleate was blood tinged. The amount of fluid gradually decreased after the first hour, and in the group receiving injections of amniotic fluid and vaccine the amounts recovered were thereafter only slightly in excess of the normal volumes. In the animals receiving sodium ricinoleate, however, the amounts of fluid were always very much higher than in either of the other two groups; and even after one week an average of 855 mg. of fluid was still present in the peritoneal space. This amount was triple that found either in the animals which had received the vaccine or in those which had received the amniotic fluid.

*Total Cells Present Per Cubic Millimeter of Peritoneal Exudate.*—Our results on the cellular content per cubic millimeter of peritoneal exudate were as follows (Table II): In a series of 100 healthy normal male rats, we found that the average number of cells in the peritoneum was 101,266 per c.mm. of fluid. One hour after the injections were given, when the volume of exudate was high, the number of cells per cubic millimeter was appreciably less and was proportional to the fluid dilution. When the volume of exudate was highest, as in the case of animals receiving sodium ricinoleate, the number of cells per unit volume was least (5,500 per c.mm.). At six hours after injection, the number of cells per cubic millimeter in rats receiving

TABLE II  
DATA ON WEIGHT OF PERITONEAL FLUID AND ITS CELLULAR CONTENTS

CONTROLS		MATERIAL INJECTED (1.0 C.C.)	NUMBER OF ANIMALS	TEST ANIMALS											
	NUMBER OF ANIMALS			HOURS AFTER INJECTION											
				1	3	6	12	24	48	72					
223*	23	Amniotic fluid concentrate	10	474	295	255	195	224	220	241					168
		Antiperitonitis vaccine	10	320	282	248	286	377	253	231					288
		Sodium ricinoleate, 2 per cent	10	3,482	3,289	2,574	1,105	1,425	1,417	1,923					855
<i>Total Cells Per Cubic Millimeter of Peritoneal Fluid (Thousands)</i>															
101.26†	100	Amniotic fluid concentrate	10	34.48	97.74	105.41	130.80	116.85	136.10	138.65					140.57
		Antiperitonitis vaccine	10	53.04	93.02	104.95	109.15	121.39	168.10	122.65					123.79
		Sodium ricinoleate, 2 per cent	10	5.50	9.73	12.23	19.85	31.12	36.75	41.34					48.34
<i>Total Cells Present in Peritoneal Fluid (Millions)</i>															
22.58†	23	Amniotic fluid concentrate	10	16.34	28.83	26.88	25.51	26.17	29.94	33.41					38.80
		Antiperitonitis vaccine	10	16.97	26.23	26.03	31.32	45.76	42.53	28.33					35.65
		Sodium ricinoleate, 2 per cent	10	19.13	31.99	31.48	31.93	44.35	52.07	79.51					41.33

\*Weight of peritoneal fluid, milligrams.

†Number of cells per cubic millimeter.

‡Total cells in peritoneum.

We determined for each rat at the time of killing the total amount of fluid present in the peritoneal space, the total number of cells present per cubic millimeter of fluid, the percentage distribution of the various cells comprising the exudate, and the total number of polymorphonuclear and mononuclear leucocytes in the peritoneum. The average of the ten determinations made for each item was accepted as representative of the conditions which existed at each period of observation throughout our study.

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nearly four times the number encountered in normal animals. Such a cellular response indicates the excessive stimulation which was induced by this irritant.

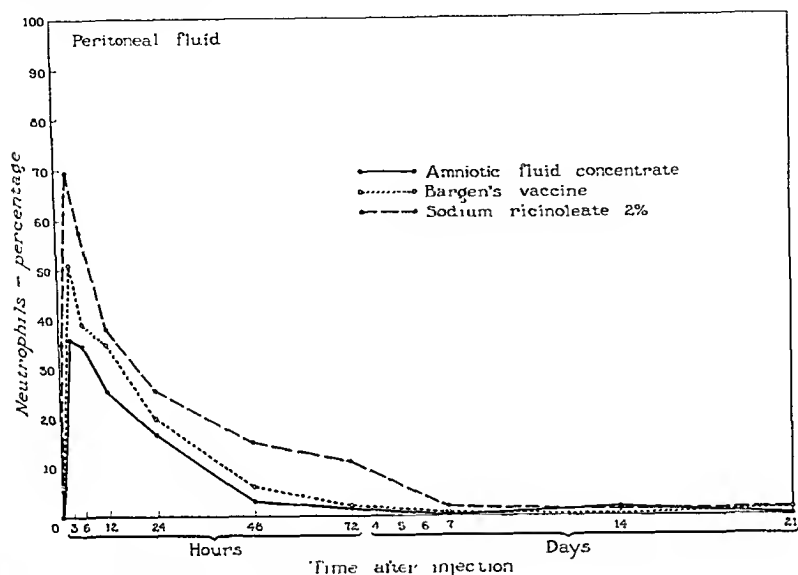


Fig. 1.—Changes in the percentage of neutrophils in the peritoneal fluid of rats at the different intervals following injection of the three substances.

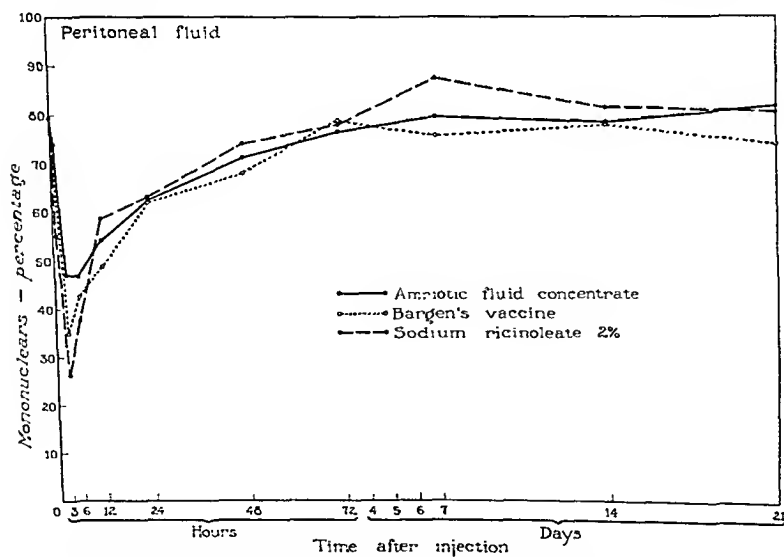


Fig. 2.—Changes in the percentage of nonnuclear cells in the peritoneal fluid of rats at the different intervals following injection of the three substances.

*The Percentage Distribution of Cells in the Peritoneum.*—Although we have computed the complete percentage distribution of the cells in the peritoneal space of all animals killed, we submit in this report the

amniotic fluid or antiperitonitis vaccine was again at control levels and the amount of fluid more closely approached the normal amounts. In contrast, the peritoneal exudate of rats receiving sodium ricinoleate contained but 12,230 cells per c.mm. at six hours following the injection, and even after one week's time the number of cells per cubic millimeter was still less than half the normal figure.

It is obvious, of course, that tabulations of cells per unit volume of fluid do not reveal the extent of cytologic changes that may occur. When dilution factors are high, then the number of cells counted per cubic millimeter is correspondingly less. Accordingly we have computed the total number of cells present in the peritoneal space of each animal and have thus derived a more adequate basis for comparison of the cytologic response incited by these three irritants.

*Total Number of Cells Present in the Entire Peritoneal Space.*—By multiplying the number of cells per cubic millimeter of fluid by the number of cubic millimeters of fluid in the peritoneal space, we derived an approximation of the total number of cells in the entire space (Table II). By multiplying our average number of cells per cubic millimeter of fluid in 100 control animals by the average total volume of fluid of twenty-one control animals, we derived a figure of 22,580,000, which we have accepted as the approximate number of cells present in the peritoneal space of each of our normal rats before injection. One hour after injection this number was found to be considerably less. Accordingly, during the hour following injection, millions of cells must have left the peritoneum, to enter either adjacent tissues or the blood stream. Counts taken on the peripheral blood at this time, however, did not indicate that there was any real significant increase in the concentration of leucocytes. At the third hour, however, a real cellular increase had occurred. This was true for all three groups, but especially so for the animals which had received sodium ricinoleate in which case an average infiltration of more than 12,000,000 cells into the peritoneum had occurred in the preceding two-hour period. This marked increase in the cellular content was maintained, although it fluctuated considerably, for the entire week, and even on the seventh day the number of cells in the body cavity of rats which had received the amniotic fluid was still increasing. Those rats which had received the antiperitonitis vaccine showed the maximal total number of exudative cells at twenty-four hours after the injection, but even at the end of the week the total number was still greatly in excess of normal values. The greatest stimulation to cellular proliferation was found in those animals which had received sodium ricinoleate. On the third day, the average of the counts made on ten rats showed a total cell content of nearly 80,000,000. This is nearly triple that found in either the group receiving amniotic fluid or that receiving vaccine, and it is

TABLE III

DATA ON PERCENTAGE DISTRIBUTION OF AND TOTAL NUMBER OF MONONUCLEAR AND POLYMORPHONUCLEAR LEUCOCYTES IN THE PERITONEAL SPACE

Percentage Distribution												
MATERIAL INJECTED (1 c.c.)		NUMBER OF ANIMALS	HOURS AFTER INJECTION									
			1	3	6	12	24	48	72	168		
Amniotic fluid concentrate	Monos.	10	74.16	47.21	47.05	54.28	62.88	72.63	77.11	80.07		
	Polys.		6.11	36.20	34.23	25.57	16.65	4.32	1.79	0.25		
Antiperitonitis vaccine	Monos.	10	68.75	34.95	42.72	48.93	62.82	68.45	79.21	76.21		
	Polys.		8.50	51.35	39.49	35.01	20.26	6.45	2.37	0.63		
Sodium ricinolate, 2 per cent	Monos.	10	55.48	26.43	37.82	54.28	63.95	74.52	78.45	87.77		
	Polys.		35.09	69.65	57.59	25.57	26.65	15.04	10.95	1.82		
Total Number of Neutrophiles* (Millions)												
Amniotic fluid concentrate		10	1.00	10.43	9.20	6.52	4.36	1.29	0.60	0.08		
		10	1.44	13.47	10.28	10.93	9.27	2.74	0.67	0.22		
Sodium ricinolate, 2 per cent		10	6.71	22.28	18.13	8.33	11.82	7.83	8.71	0.75		
Total Number of Mononuclear Cells† (Millions)												
Amniotic fluid concentrate		10	12.11	13.61	12.65	13.85	16.45	21.75	25.76	31.07		
		10	11.67	9.17	11.12	15.28	28.75	29.11	22.44	27.17		
Sodium ricinolate, 2 per cent		10	10.61	8.45	11.91	12.93	28.36	38.80	62.38	36.28		

\*Number of neutrophils in peritoneal cavity of normal rat =  $101.266 \times 233 \times 0.08$  per cent = 18,065.†Number of mononuclear cells in peritoneal cavity of normal rat =  $101.266 \times 223 \times 79.77$  per cent = 18,013,915.

data pertaining to the percentage distribution of only the mononuclear and polymorphonuclear leucocytes. Basophilic and eosinophilic leucocytes were always present, but their percentages were essentially unaffected by these substances. We have not separated lymphocytes from other mononuclear cells, but we have grouped the histiocytes or elasmatocytes of the exudate with the lymphocytes and have called them "mononuclear" leucocytes. On the basis of 100 counts on 100 animals, we concluded that the distribution of cells in our series of rats before injection was as follows: mononuclear leucocytes, 79.77 per cent; polymorphonuclear leucocytes, 0.08 per cent; basophiles, 5.25 per cent; and eosinophiles, 14.75 per cent.

The data assembled from our tabulation of the percentage distributions of the mononuclear and polymorphonuclear leucocytes in the peritoneal spaces of all animals for the seven days following injection have been condensed into Table III and shown graphically in Figs. 1 and 2. The polymorphonuclear cells appeared in the exudate soon after the injections were made, and, at one hour, percentages of 6.11 and 8.5, respectively, were found for the amniotic fluid and vaccine groups. The neutrophile response to the presence of sodium ricinoleate was most marked. Even at one hour, 35.09 per cent of all cells were polymorphonuclears; at the third hour, 69.65 per cent of all the cells were polymorphonuclears. The neutrophile response to the vaccine was much greater than to amniotic fluid, and in all three groups of animals the highest percentages were reached at three hours following injection. Following this period there was a progressive decline in the percentage of neutrophiles in the exudates, and after one week percentages which were essentially normal were restored. Conversely, the percentage of mononuclear leucocytes progressively increased after the third hour; and on the third day percentages comparable with those of our control group were obtained. Even higher percentages than those were found in the animals receiving amniotic fluid and in those receiving sodium ricinoleate at the end of the week.

*Total Mononuclear and Polymorphonuclear Cells Present in the Peritoneal Space.*—It is obvious that the percentage distribution will not adequately portray the extent of change which occurred in the exudate relating to the total numbers of mononuclear cells and neutrophiles which were present at the successive intervals following injection. Accordingly, using our data on the total number of cells and percentage distribution, we computed the total numbers of mononuclear cells and neutrophiles which were present in each animal killed at the various intervals following the injection of the three substances. From our control data we had computed that the number of mononuclear cells present prior to injection was more than 18,000,000, and that the number of polymorphonuclear cells was slightly in excess of 18,000. The

in all three groups of animals examined, but in those which had received ricinoleate the number of neutrophils was more than double that found in those receiving amniotic fluid. The rise in the number of mononuclear cells began about the sixth hour after injection. The peak of 62,000,000 cells was found in those animals receiving ricinoleate, and it occurred at the end of the third day. The peak of mononuclear infiltration in animals receiving the vaccine occurred on the second day; whereas, at the end of the week the trend in the absolute numbers of mononuclears was still upward in those animals which had received amniotic fluid.

#### COMMENT

In this study we have attempted to quantitate some of the changes which occur in the peritoneal cavity of rats after the intraperitoneal injection of 1 c.c. of concentrated amniotic fluid, antiperitonitis vaccine, or of 2 per cent sodium ricinoleate. We have determined the total amount of fluid present, and the percentage distribution and total number of exudative cells present at varying intervals after injection of these three agents.

The results indicate conclusively that all three substances caused a marked increase in the amount of fluid exudate, the increase being much more marked in animals receiving sodium ricinoleate than in those receiving either amniotic fluid or vaccine. Furthermore, the results show that there were in all animals marked influxes of leucocytes into the exudate. In the early period these cells were predominantly polymorphonuclear, but from the twelfth hour onward they were predominantly mononuclear and consisted of monocytes, lymphocytes, and histiocytes. As in the extent of fluid response, the numbers of cells in the exudates of animals which received ricinoleate were usually greatly in excess of those found in animals of the other two groups.

The rate at which these changes in the amount of fluid and in the cellular content occurred, the magnitude of these changes, and the length of time they persisted varied with the material employed.

Conclusions regarding the significance of these results, both as regards the mechanism of response of the peritoneum and the use of these peritoneal irritants in the prevention of peritonitis, must await the results of further investigation. Certain questions which arise concern the life history of these cells which appear in the exudate. Where they come from, how they enter the peritoneum, and how long they remain in the peritoneum are questions which thus far have been answered only in part. Another question is, what is the source of the fluid portion of the exudate? Does it arise from the entire serous surface, or is it mainly elaborated by the parietal or the visceral peritoneum?



data on these changes (Table III and Figs. 3 and 4) show that, at one hour, more than 6,000,000 polymorphonuclear cells had entered the

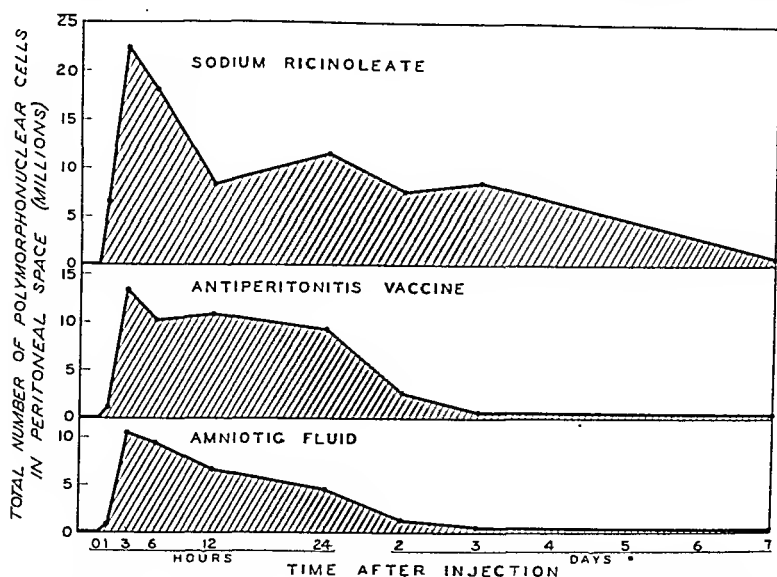


Fig. 3.—Changes in the total number of polymorphonuclear cells in the peritoneal fluid of rats at the different intervals following injection of the three substances.

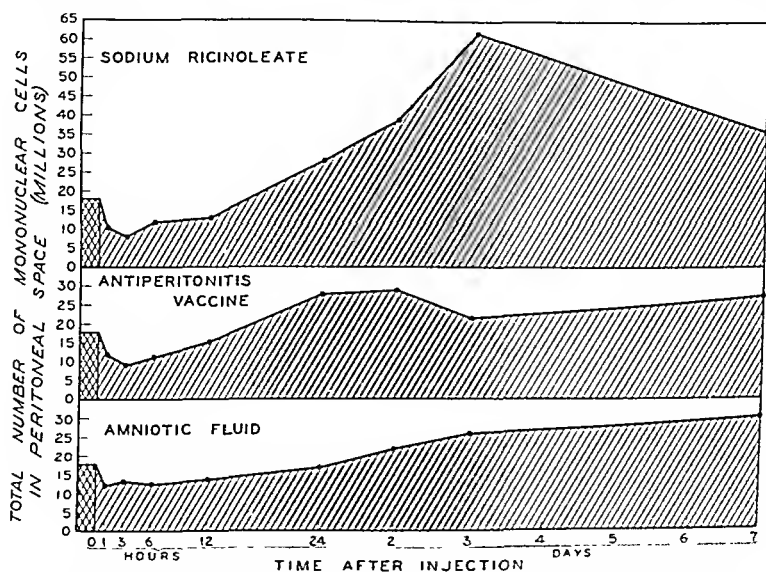


Fig. 4.—Changes in the total number of mononuclear cells in the peritoneal fluid of rats at the different intervals following injection of the three substances.

exudate of those animals receiving sodium ricinoleate and that the number of mononuclear cells was less than when the soap was injected. At the third hour, the infiltration of neutrophils had reached its height

5. Correspondingly, the number of neutrophilic granulocytes was always higher, except at the twelfth hour, in those animals receiving ricinoleate than in those of the other two groups.

6. The number of histiocytes in the peritoneal fluid of animals receiving ricinoleate, at seventy-two hours after injection, was nearly triple that found in animals of the other two groups.

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While it would be anticipated that a reaction of the peritoncum to a noninfectious irritant would have a protective action against a subsequent infection, as the experimental work of Herrmann, Morton, and others would indicate, it must be admitted that, at present, it is almost impossible to standardize such a process as peritonitis.

We believe that investigations of the sort we are here reporting are of value in filling some of the gaps in our knowledge of peritoneal reactions and of help in supplying the answers to some of the questions enumerated.

#### SUMMARY AND CONCLUSIONS

This report covers a study of the quantitative and qualitative cellular responses of the normal peritoneums of white rats to three substances: (1) concentrated amniotic fluid, (2) antiperitonitis vaccine, and (3) 2 per cent sodium ricinoleate. One cubic centimeter of each preparation was given intraperitoneally to eighty rats, and ten animals in each group were killed at each of the following intervals after injection: 1 hour, 3 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, and 1 week.

The following conclusions are indicated:

1. As evidenced by the fluid exudate produced, sodium ricinoleate was found to be far more irritating to the peritoneum than either amniotic fluid or the vaccine. In one hour, eight to ten times as much straw-colored fluid was produced in rats receiving the ricinoleate as in rats of either of the other two groups. Large amounts of fluid persisted even after one week.

2. The total number of cells per cubic millimeter of peritoneal fluid was always less in animals which had received sodium ricinoleate. This is because of the large dilution factor. As between animals receiving amniotic fluid and those receiving vaccine, there were no outstanding differences.

3. The data on the total number of cells in the peritoneal spaces of these animals show that ricinoleate causes an excessive proliferation of histiocytes. On the third day the number of cells in animals receiving ricinoleate was nearly triple that found in animals receiving either amniotic fluid or vaccine. This indicates the enormous stimulative action of sodium ricinoleate.

4. With respect to the percentage distribution of cells in the peritoneal space, the data show that the neutrophile response during the first six hours after injection is much greater in animals receiving ricinoleate than in those receiving either of the other two substances. Likewise, neutrophilic granulocytes remain in the peritoneum very much longer in animals which have received ricinoleate.

# AN EXPERIMENTAL STUDY UPON THE PREVENTION OF ADHESIONS ABOUT REPAIRED NERVES AND TENDONS\*

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THE success of many nerve and tendon operations has been prevented by scar tissue which grows about the suture line from the surrounding injured structures. More often than not, the normal muscle plane has been destroyed at the time of injury and only dense fibrous tissue remains. It is this lack of a normal nerve bed or gliding tendon mechanism which creates an important surgical problem.

Many attempts have been made to find a substance which might be used to protect the line of suture, which would form a bed free of adhesions or a smooth gliding surface for a tendon. The variety of materials used clinically and in animal experiments includes fat, cartilage, sterile vaseline, autoplasmic fascia, rabbit's vena cava, Cargile membrane, hardened appendices, tubes of magnesium, celloidin, and decalcified bone, gold and silver foil, egg membrane, and formalized arterial sheaths. The results obtained have not been uniformly successful nor have they been duplicated in all instances by other investigators.

J. S. Davis<sup>1</sup> used free fascial transplants with the muscle or inner surface exposed about nerve sutures. Although there was no constriction of the caliber of the nerve after one month, there was very little motion possible within this new sheath. Lewis<sup>2</sup> used fascia and large fat transplants with a fair degree of success about nerve sutures after concluding that fascia alone contracts and becomes adherent. He stated that fat heals in position with but little reaction of the foreign body type and causes the least amount of adhesions. However, Huber<sup>3</sup> found that free autogenous fat transplants were replaced by dense fibrous tissue. Stewart<sup>4</sup> suggested that fat and not fascia should be employed in a neurolysis because fascia produces adhesions which shrink and compress the nerve. In the past year Mayer and Ransohoff<sup>5</sup> have constructed a sheath which resembles the normal tendon sheath lining from tubes of celloidin. They implanted these tubes at the site of the old injury and proposed tendon suture. Six weeks later the proximal tendon stump was threaded through the celloidin tube which was gently removed leaving a smooth glistening

\*The materials used in these experiments were furnished by Curity Laboratories of the Lewis Mfg. Co., Walpole, Mass.  
Received for publication, July 14, 1937.

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week, but grossly the same mucoid appearance existed with less edema than was present at the end of 5 days. There was little evidence of any one of the materials after the third week and none after the fourth week. The beef cecum was found at the end of the sixth week macroscopically as a minute mucoid patch and microscopically by the presence of leucocytes and lymphocytes. Allantoic membrane was most quickly absorbed and could not be found after the third week.

In a second series of experiments, a plane of cleavage was outlined between the biceps femoris and the semitendinosus muscles in ten dogs. The epimysium of the inner surface of each muscle was denuded by scraping with a scalpel until it was dull and bled slightly. Sheets of allantoic membrane (beef and human), cellophane, and rubber latex were inserted between the muscles, which were then allowed



Fig. 2.—Cross-section of sciatic nerve of dog which was covered by allantoic membrane and a pedicle flap of fat and allowed to remain in situ 29 days. The nerve was found lying free in the center of the fat cells without evidence of new fibrous tissue formation and no evidence of the membrane.

to fall together. It was found that after the sixth week allantoic membrane left the most definite plane of cleavage, which allowed the muscles to be separated easily down to the sciatic nerve, while human\* and beef amniotic membrane caused a definite obliteration of this plane of cleavage and the muscles were found grown together firmly. Cellophane and rubber latex in thick sheets caused not only severe tissue reaction as indicated by the presence of thick serum in the wound, but there was a definite obliteration of the intermuscular space. In the control experiments, the muscles adhered firmly by dense fibrous tissue.

\*Human amniotic membrane was used in these experiments to determine whether or not there was some property of amniotic membrane in utero which prevents adhesions and which may have been destroyed in the preparation or sterilization of the beef membranes. The human amniotic membrane was secured at cesarean section and placed in sterile saline solution. It was then washed and used in all the human amniotic experiments without alteration except where indicated.

membrane. The tendon was sutured within this new gliding mechanism. Their tubes were made of proxylin and acetone placed in the incubator and allowed to harden over a period of three to five months. More recently, absorbable tubes of catgut membrane have been suggested by Bowen.<sup>6</sup>

Conflicting reports of this character may be found in the literature upon every one of the substances used in an effort to solve this problem. We have confined our study to an experimental investigation of the following materials:

*Beef amniotic membrane*, which is found in all amniote vertebrates and which is a purely protective structure in utero, having an inner ectodermal and an outer mesodermal layer.

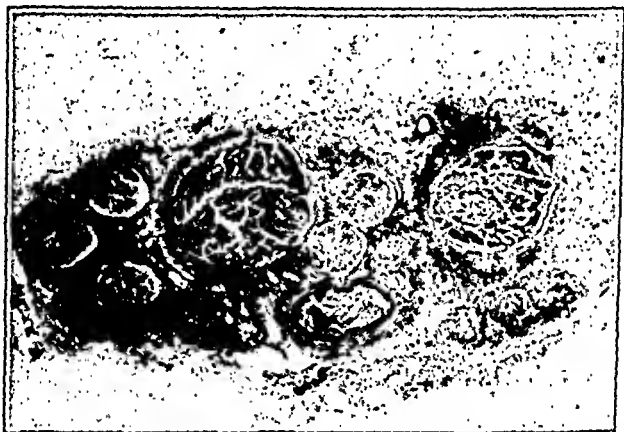


Fig. 1.—Cross-section of sciatic nerve of dog about which allantoic membrane was placed and allowed to remain in situ 61 days. There is no evidence of the membrane but a thick layer of fibrous tissue, infiltrated with round cells, surrounds the nerve trunk.

*Beef allantoic membrane*, which is an evagination of the hind gut and which is lined with entoderm and covered with splanchnic mesoderm.

*Sheet catgut*, derived from the submucosa of the jejunum, stretched, dried, and chemically sterilized.

*Beef cecum*, chemically sterilized mucosa of the cecum.

*Commercial cellophane* (cellulose acetate) and *rubber latex*.

Our first problem was to determine the irritative property of each of these structures. Two-centimeter squares of each membrane were placed between the fascia and rectus abdominis muscle of dogs and allowed to remain in situ for various periods of time ranging from 5 to 53 days. The region of implantation was then examined for the signs of inflammation and evidence of absorption. At the end of 5 days, each of the materials was still present but in a mucoid form. Microscopically, the most marked reaction was present in the second

week, but grossly the same mucoid appearance existed with less edema than was present at the end of 5 days. There was little evidence of any one of the materials after the third week and none after the fourth week. The beef cecum was found at the end of the sixth week macroscopically as a minute mucoid patch and microscopically by the presence of leucocytes and lymphocytes. Allantoic membrane was most quickly absorbed and could not be found after the third week.

In a second series of experiments, a plane of cleavage was outlined between the biceps femoris and the semitendinosus muscles in ten dogs. The epimysium of the inner surface of each muscle was denuded by scraping with a scalpel until it was dull and bled slightly. Sheets of allantoic membrane (beef and human), cellophane, and rubber latex were inserted between the muscles, which were then allowed



Fig. 2.—Cross-section of sciatic nerve of dog which was covered by allantoic membrane and a pedicle flap of fat and allowed to remain *in situ* 29 days. The nerve was found lying free in the center of the fat cells without evidence of new fibrous tissue formation and no evidence of the membrane.

to fall together. It was found that after the sixth week allantoic membrane left the most definite plane of cleavage, which allowed the muscles to be separated easily down to the sciatic nerve, while human\* and beef amniotic membrane caused a definite obliteration of this plane of cleavage and the muscles were found grown together firmly. Cellophane and rubber latex in thick sheets caused not only severe tissue reaction as indicated by the presence of thick serum in the wound, but there was a definite obliteration of the intermuscular space. In the control experiments, the muscles adhered firmly by dense fibrous tissue.

\*Human amniotic membrane was used in these experiments to determine whether or not there was some property of amniotic membrane *in utero* which prevents adhesions and which may have been destroyed in the preparation or sterilization of the beef membranes. The human amniotic membrane was secured at cesarean section and placed in sterile saline solution. It was then washed and used in all the human amniotic experiments without alteration except where indicated.



A third series of experiments were performed on the sciatic nerves of dogs. Under ether anesthesia the sciatic nerve was exposed in the lower half of the thigh for a distance of two inches. The nerve was roughened with a scalpel until the glossy epineurium was removed and oozing of blood was present. Silk sutures were placed in the epineurium above and below to simulate an anastomosis. Each of the five types of membrane was wrapped about the denuded area of the nerve and the dogs were sacrificed at intervals of from 9 to 82 days. In control experiments the nerve was found firmly adherent to the surrounding tissue, and microscopically a thin layer of fibrous tissue was present about the nerve trunk.

In ten of these experiments, allantoic membrane was used and allowed to remain in situ from 9 to 65 days. Grossly, the nerves were thickened but could be removed from the muscle bed with ease. After

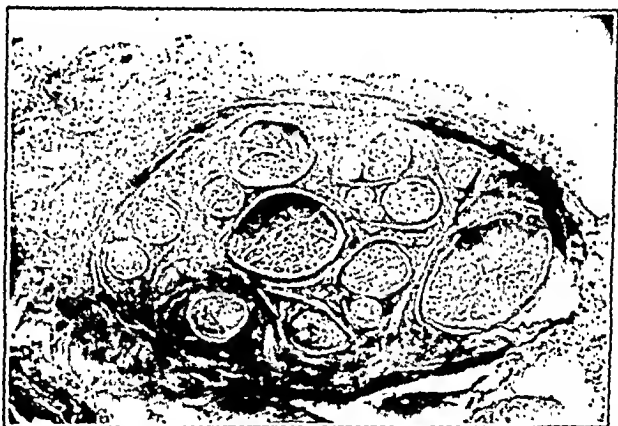


Fig. 3.—Cross-section of sciatic nerve of dog covered with human amniotic membrane, allowed to remain in situ 39 days. There was a definite proliferation of fibrous tissue and marked infiltration of round cells.

the first week the nerve was covered by a loose areolar tissue, while at the end of 7 to 9 weeks, there was no evidence of the membrane grossly, or microscopically. However, a thick layer of fibrous tissue infiltrated with round cells surrounded the nerve trunk so that the nerve fasciculi were constricted. Many small new blood vessels were present in this layer of scar tissue. In one dog, a pedicle of fat was placed about the allantoic membrane. Fine adhesions developed between the fat and muscle, but the nerve was found lying free in the center of the fat cells without evidence of new fibrous tissue formation.

Beef amniotic membrane was used to cover the sciatic nerve of five dogs and allowed to remain in situ from 9 to 65 days. The nerves could not be removed from their beds without injuring the tissue at any time and the immediate covering of the nerve could not be determined grossly. Microscopically, there was a definite proliferation of

fibrous tissue and a marked infiltration with round cells. Fat was also placed about this membrane in one dog and became adherent both to the nerve and surrounding tissue. Human amniotic membrane was used in seven instances and allowed to remain from 39 to 56 days. These nerves were all firmly fixed in position and could not be removed without dissection. Microscopically, there was very little difference between the human and beef amniotic membranes, but if any, the human membrane caused more reaction.

Beef cecum was used about four nerves and allowed to remain in situ from 18 to 26 days, resulting in definite adherence to the surrounding structures. Microscopically, thick dense fibrous tissue with numerous round cells and new blood vessels was present about the nerve trunk.

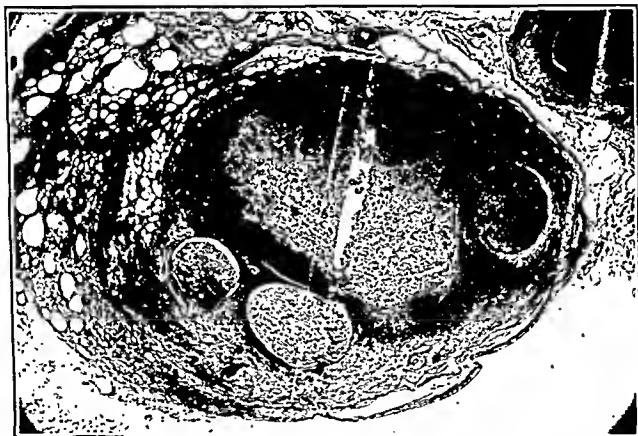


Fig. 4.—Cross-section of sciatic nerve of dog covered with sheet catgut, which was allowed to remain in situ 42 days. There was a thick layer of scar tissue intimately attached to the nerve bundles.

Sheet catgut membrane was used in five dogs and allowed to remain from 13 to 82 days. The nerves could not be removed except by sharp dissection. There was marked thickening of the nerve and its surrounding tissue. Microscopically, there was a thick layer of scar tissue after the third week which was intimately attached to the nerve bundles. Fat placed about the sheet catgut did not prevent the formation of adhesions as was true in the case of the allantoic membrane.

#### SUMMARY

From the gross and microscopic evidence, it was apparent that allantoic membrane caused the least reaction about the traumatized nerve and protected the nerve from the growth of scar tissue from the surrounding tissue bed. Even better results were obtained with the use of allantoic membrane covered with a flap of fat. Beef and human amniotic membrane produced definite adhesions about the nerve and

fibrous thickening to the same degree as control experiments. Beef cecum and sheet catgut produced thick fibrous adhesions which persisted up to 42 and 82 days and proved to be the least desirable of the membranes studied.

A fourth series of experiments was carried out upon the tendons with and without sheaths in dogs. The Achilles tendon of dogs has no definite sheath but is covered by a paratenon. The peritendinous tissue is important in the reparative process of the tendon in that it provides a blood and lymphatic supply to the injured tendon, and finally after this outer sheath serves its initial function it loosens and takes over a gliding function.<sup>7</sup> In tendons with sheaths, as in the foreleg of the dog, a mesotendon which contains the nutrient blood vessels is attached on the deep surface of the tendon. No matter how carefully one may repair a divided tendon, the endothelial cells lining



Fig. 5.—Extensor carpi ulnaris tendon of dog. Sheath was opened, tendon cut, sutured, denuded of endothelial surface, and covered with allantoic membrane, which was allowed to remain in situ 37 days. There is no evidence of the membrane, and the sheath of the tendon is not adherent. This compared favorably to the control specimen in which no membrane was used about the tendons with sheaths.

the tendon sheath and surface of the tendon are rubbed off. This predisposes to adhesions and fibroblasts grow out from the subendothelial tissues of the sheath and tendon and unite these structures. However, when the limb is freed and motion begins, the stretching causes an elongation of the connective tissue cells which break and form flat endothelial cells. This process forms a new gliding mechanism.<sup>8</sup>

The following experiments were performed to determine the value of various membranes in forming a sliding mechanism following tendon repair. The Achilles tendon of dogs was exposed by a curved incision on the lateral surface of the leg to prevent adherence of the scar to the tendon. The peritendinous tissue with its vascular plexus was retracted and the endothelial covering of the tendon was removed by scraping the tendon with a scalpel until it was dull and lusterless.

The tendon was then severed transversely and sutured with silk. A thin sheet of each of the various membranes was carefully wrapped about the denuded and sutured tendon and the peritendineum was not sutured but was allowed to fall back over the membrane. Casts were applied to the legs for two to four weeks and the dogs were sacrificed at intervals varying from 9 to 89 days. Comparative studies were also made on the extensor carpi ulnaris and extensor digitorum tendons. The sheaths were opened and the tendon was denuded of its endothelial covering for one inch. The tendon was then sectioned transversely and sutured with black silk. The suture line and denuded tendon were covered with a layer of one of the four types of membrane. The extensor tendon in the opposite foreleg was used as a control in each instance. The tendon sheaths were not sutured but allowed to fall back into place over the sutured tendons. In this



Fig. 6.—Achilles tendon of dog cut, sutured, denuded of endothelial surface, and covered with beef amniotic membrane, which was allowed to remain in situ 15 days. Paratendinous tissue is invaded by numerous leucocytes and the tendon is fragmented.

group of experiments a layer of commercial cellophane (cellulose acetate) was used in several dogs to compare with the animal membranes.

Allantoic membrane was placed about the Achilles tendon of fourteen dogs and allowed to remain in situ from 5 to 82 days. During the first three weeks the tendons were markedly thickened, soft, and presented a dull gray appearance. The peritendinous tissue was thickened to three times its normal diameter. From the fourth to the ninth weeks the tendons became thinner and firmer and the peritendinous sheath was also reduced in thickness. However, at this time the tendon could be moved freely beneath the skin and function was not impaired. On removal of the tendon, it came away from its position beneath the skin easily. The microscopic examination revealed fine attachments of the surrounding tissue to the tendon, espe-

cially about the intratendinous septa even up to the seventh week. In one dog the combination of allantoic membrane covered with a flap of fat was allowed to remain about the Achilles tendon for 82 days. At the end of that time, the tendon could not be separated from the skin due to the dense adhesions present.

Allantoic membrane was inserted about tendons with sheaths and examined after 37 to 89 days. The tendons were adherent to the overlying sheath by easily broken, thin adhesions but moved easily within the sheaths at the end of 89 days. Microscopically, there was an endothelial covering to this tendon and lining of the sheath. This group compares favorably to the control experiments in which no membrane was used about tendons with sheaths.

Beef amniotic membrane was used about eleven Achilles tendons and human amniotic membrane about two. The materials were al-



Fig. 7.—Thirty-seven-day control specimen in which Achilles tendon was sectioned, sutured, and denuded of endothelial covering, but in which no protective membrane was used.

lowed to remain in situ from 5 to 82 days. Grossly, the tendons did not move easily beneath the skin and the surface was dull and roughened. Early the tendons were thickened and gelatinous, while after 49 days there was poor healing of some tendons and the peritendinous tissue was thickened. Human amniotic membrane in larger sheets caused a marked enlargement in the regional lymph nodes and the tendons were fixed to the surrounding structures. Microscopically, the tendon was fragmented and the peritendinous tissue was invaded by numerous leucocytes.

Amniotic membrane was used about five tendons with sheaths and allowed to remain in situ from 37 to 70 days. The tendons moved within the sheath after the sixty-fifth day, but in those tendons where the sheath was destroyed, dense lusterless adhesions were present and motion was limited.

Beef cecum was used about six tendons and allowed to remain in situ from 14 to 37 days. In all these tendons there was marked swelling with poor healing in the first three weeks. The tendons did not separate from the surrounding structures and microscopically there was fibrous tissue present about them.

Catgut in sheets was used about four Achilles tendons and allowed to remain in situ from 27 to 82 days. The late results up to 82 days were similar to those found in control experiments, namely, fixation of the tendon peritendinous tissue and skin about planes of cleavage.

Commercial cellophane was used about tendons with sheaths in 6 dogs. The cellophane was sterilized by immersing in tubing fluid (alcoholic solution of potassium mercuric iodide). There was swelling and fluctuation of the skin over these tendons, and thick serosanguineous fluid escaped upon opening the tendon sheath. The cello-

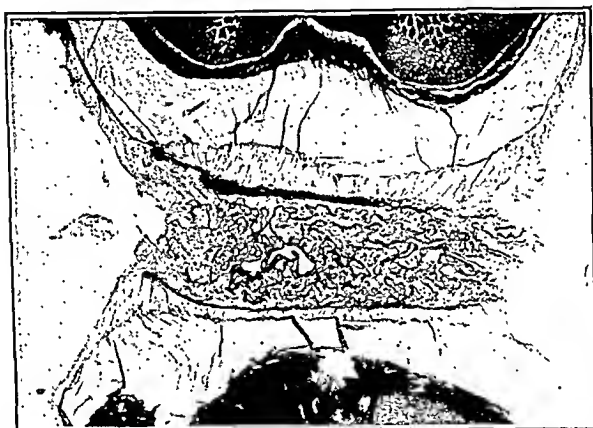


Fig. 8.—Cross-section of two loops of jejunum denuded of their peritoneal surfaces. A layer of beef cecum was inserted between the loops, which were then tacked together and allowed to remain in situ 15 days. Invasion of membrane by small round cells. Ingrowth of scar tissue from subserosa permanently fixed opposing surface of bowel.

phane originally inserted was still present. Three tendons were covered with very thin cellophane and allowed to remain in situ 83 days. There was no reaction within the sheath and the tendon moved easily. The surface of the tendon was well lubricated and presented a shiny appearance. The outer surface of the sheath where it had been elevated from its bed was adherent.

#### SUMMARY

Achilles tendons sectioned, sutured, and not covered with any membrane heal with definite fixation to their surrounding structures by fibrous adhesions which do not loosen in dogs even as late as the eighth week. Allantoic membrane used over Achilles tendons allows for a peritendinous sheath which is less adherent to the tendon. While not al-

together free of adhesions on microscopic examination, grossly there is free motion of the tendon. The use of beef amnion is not as efficient as allantoic membrane but forms a less adherent gliding mechanism than the control experiments.

Human amniotic membrane, untreated, was definitely inferior to allantoic membrane. The use of beef cecum and catgut in sheets causes dense adhesions, and in some instances the use of catgut causes firmer fixation than that found in the control experiments.

Injured tendons in which the sheath was not destroyed healed with an excellent gliding mechanism after five weeks. The insertion of animal membranes about these tendons forms a gliding mechanism which is inferior to the control experiments in which the sheath is left intact although allantoic membrane is the most favorable. Cellophane in very thin sheets forms an inner gliding surface which is smooth and the tendon heals well, but the outer surface of the tendon sheath is adherent to the surrounding structures.

Adhesions are the most frequent sequel to operations in the abdominal cavity, where the shiny peritoneal surface is denuded. The following experiments were carried out in ten dogs to determine the adhesion prevention properties of these membranes in the abdomen.

The abdomen was opened in the midline and various surfaces of the stomach, jejunum, and ileum, as well as anterior parietal peritoneum, were scarified until they presented a dull lusterless appearance and an oozing bloody surface. The surface of the ileum was then covered with one type of membrane and fixed with four interrupted sutures to a similarly denuded surface of the stomach, jejunum, ileum, or anterior parietal peritoneum. Allantoic, beef amniotic, beef cecum, and sheet catgut were used in five dogs and allowed to remain in situ from 14 to 49 days. The loops of bowel which were opposed were found adherent and could not be disengaged by gentle traction. There was no apparent difference in the results with any of the four membranes. Microscopically, there was invasion of the membrane by small round cells, and the surfaces of the bowel walls were intimately attached. Since this procedure of tacking the opposing denuded surfaces together after interposing the animal membrane did not allow for free motion of the bowel, the results were open to question. It was suggested, Dr. H. L. Johnson, of Boston, that the denuded surfaces would be prevented from disengaging themselves by the fixation sutures when the inflammatory reaction had subsided and the process of repair had begun. This would allow for an ingrowth of scar tissue from the subserosa and thus intimately and permanently fix the opposing surfaces.

Therefore, in another series of experiments the parietal peritoneum of the anterior abdominal wall was scarified and the right half was covered with human amniotic membrane while the left half was left

unprotected. Ten inches of bowel were similarly scarified and two inches of the bowel surface were covered with the same type of membrane. The dogs were sacrificed at the end of 49 and 70 days. It was found that no adhesions formed between the scarified bowel and other viscera, or to either half of the anterior abdominal wall. In another experiment the same procedure was employed except that the thick mucous covering of the amniotic membrane was removed and discarded, leaving a thin transparent glistening membrane which was placed over the right half of the parietal peritoneum. At the end of 70 days, it was found that the omentum and bowel were adherent to the denuded left half of the anterior abdominal wall and to the patch of mucus-free amniotic membrane.

The same type of experiment was carried out on two dogs with the use of allantoic membrane which was allowed to remain in situ for 65 days. The bowel and omentum were found to be adherent to the uncovered parietal peritoneum and the denuded bowel was adherent to other loops of bowel but the portion of bowel and parietal peritoneum covered with membrane remained free of adhesions.

Thus, it would appear that the presence of human amniotic membrane with its mucous surface intact prevents the formation of adhesions within the peritoneal cavity of dogs. Amniotic membrane devoid of a mucous surface does not prevent the formation of adhesions and allantoic membrane prevents adhesions only to the extent of the size of the patch of membrane used.

#### CONCLUSIONS

1. When allantoic and amniotic membranes, sheet catgut, and beef cecum are placed between muscle and fascia in dogs, they are absorbed and are found to be least irritating in the order named.

2. Allantoic membrane has the property of lessening the amount and degree of adhesions which form about injured nerves, tendons without sheaths and denuded peritoneal surfaces. Beef and human amniotic membranes are definitely inferior to allantoic membrane when used about nerves and tendons as an agent in lessening the formation of adhesions.

3. Amniotic membrane with its mucous surface intact has the property of preventing adhesions between denuded peritoneal surfaces. Allantoic membrane prevents the formation of adhesions between denuded peritoneal surfaces limited to the size of the membrane used.

4. Beef cecum and sheet catgut allow adhesions to form about injured nerves and tendons and in the peritoneal cavity approximately to the same degree. The results of this group of experiments show more adherence and the production of greater amount of scar tissue in the surrounding structures than in the control experiments.



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# THE MODERN TREATMENT OF VARICOSE VEINS

WITH A REVIEW OF 285 CASES

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VARICOSE veins of the lower extremities were found in 285 cases among over 9,000 admissions to the Hutchinson Memorial Clinic of Tulane University from October, 1932, to May, 1936. Two hundred and forty-seven of these cases were females and 38 were males. Of the 247 females, 152 were treated in the Department of Obstetrics and varicose veins was simply an associated diagnosis, pregnancy being the main reason for their admission to the Clinic. The ratio of females to males in the entire series is 6.5 to 1, and the ratio of nonpregnant females to males is 2.5 to 1. Of the 247 females with varicosities, 62.6 per cent (152) accompanied pregnancy. That pregnancy is a very important factor in the production of varicose veins is further corroborated by consideration of age periods. The average age of the males with varicose veins was 48.1 years. The average age of the nonpregnant females with varicose veins was 47 years; whereas, that of the pregnant females with varicose veins was 30.6 years. The average age of the entire series of females was 36.9 years, and the average age in the entire group was 38.4 years. Thus, the average age of females is 11 years younger than the average age of males, and the average age in pregnant females with varicosities is 17.5 years younger than the average age of males. The average age of the nonpregnant female patients (47 years) and the male patients (48.1 years) is approximately the same.

The youngest male patient was 18 years of age and the oldest male patient was 79 years of age; whereas, the corresponding figures for females were 18 and 70 years, respectively. It is appreciated that the female and male groups are not exactly comparable, because in the majority of males in which the diagnosis of varicose veins was made the varicosities were the principle lesion; whereas, in most of the females the varicosities were of secondary importance. Heredity is an important factor in the production of varicose veins, as illustrated by our cases. The majority of patients stated that their father, their mother, or both, had varicose veins. A small group consisting of a mother, a sister, and a daughter all having marked varicose veins of the lower extremities had themselves noted a definite family predisposition to varicosities.

Received for publication, June 5, 1937.

Of the 285 cases with diagnosed varicosities in this series, only 100 were seen in the Department of Surgery. It is the routine in examining these patients to test the circulation in the varicosities of the lower extremities by three methods: (1) the Trendelenburg test,<sup>1</sup> (2) the Perthes test,<sup>2</sup> and (3) the combined tourniquet test, described by Mahorner and Ochsner<sup>3</sup> (Figs. 1, 2, and 3). Our test consists of having the patient walk with the extremities exposed so that the degree and extent of the varicose veins can be determined. At first no tourniquet is applied to the extremity, but after determining the type, degree, and location of the varicosities, a tourniquet is applied around the upper third of the thigh sufficiently tight to obstruct the return venous flow in the superficial veins, including the internal saphenous. The character of the varicosities is again determined while the patient is walking.

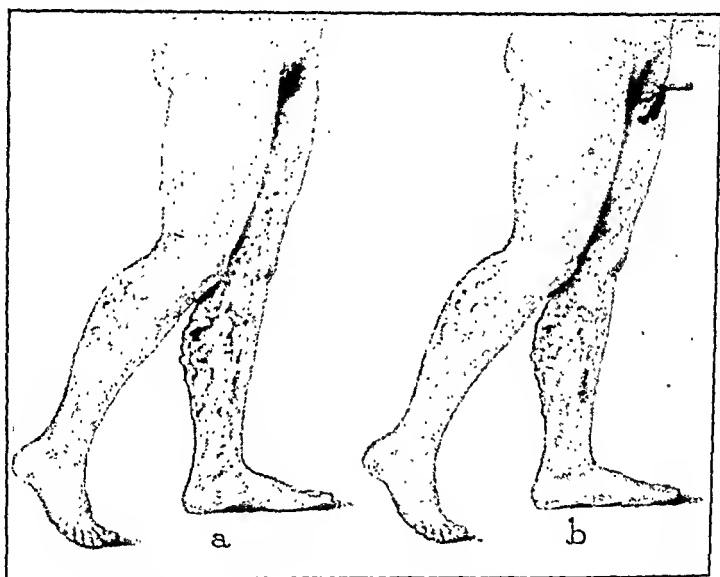


Fig. 1.—Drawings illustrating the comparative tourniquet test (Mahorner and Ochsner, Arch. Surg. 33: 479, 1936) for determining the competency of the valves of the communicating veins between the deep and the superficial systems of the thigh. The patient walks at a normal gait, and the prominence of the veins of the calf is noted (a). Thereafter, the tourniquet is applied to the upper third of the thigh (b), sufficiently tight to compress the superficial veins. Observations are made for changes in the appearance of the veins of the calf. At other times the tourniquet is similarly applied to the middle and the lower thirds of the thigh (c and d). The patient walks over the same course, and the prominence of the veins is noted. If the valves of all of the deep communicating veins of the thigh are competent and the result of the Trendelenburg test is positive, there is diminished prominence of the veins of the calf when the patient walks with the tourniquet around the upper third of the thigh. If the valves of the communicating veins are incompetent, there is little or no change because the blood spills through the incompetent communicating veins from the femoral to the long saphenous vein. When the tourniquet is below the lowest communicating vein of the thigh in which the valves are incompetent (d), the veins of the calf become less prominent. In this instance high ligation alone is not sufficient, and low ligation also must be performed to prevent retrograde flow through communicating veins. In b, slight improvement is shown over that indicated in a, in a case in which the blood spills through the communicating veins below the level of the tourniquet. In c, slight improvement (diminution in prominence) in the veins of the calf is shown, and in d the greatest improvement appears. If the improvement shown in b were as great as that illustrated in d, the test would indicate competency of the communicating veins of the thigh.

Similar observations are made with the tourniquet applied around the middle and lower thirds of the thigh, respectively. There will be a diminution in the degree of prominence of the varicosities when the patient walks with the tourniquet applied if the deep venous circulation is adequate. This improvement may be so marked that the varicosities disappear practically entirely, in which instance it is graded as 4. Lesser degrees of improvement are graded as 3, 2, and 1. If the improvement is as great with the tourniquet around the upper third of the thigh as it is with the tourniquet around the lower third, it is obvious that there is no leak below the main opening of the internal saphenous vein into the femoral; i.e., the valves of the communicating vein between the deep and superficial systems are competent, not permitting blood to flow from

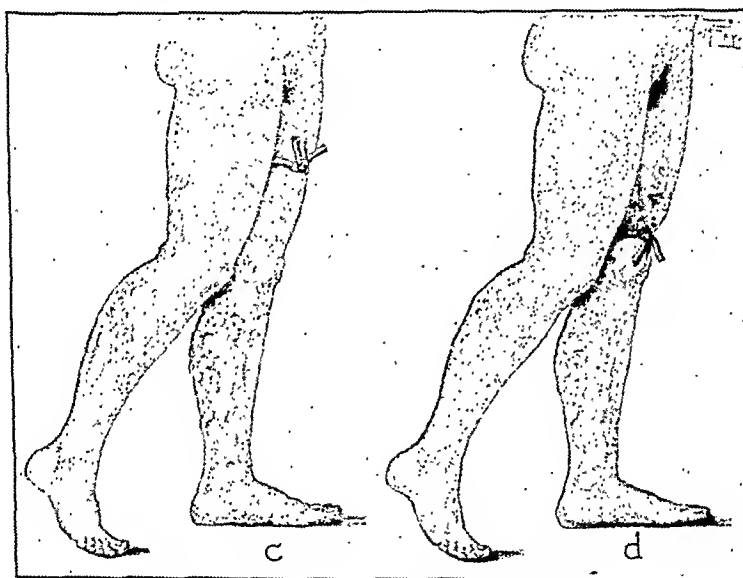


Fig. 1c and d.—See opposite page for legend.

the deep system into the superficial below the main opening of the long saphenous. In only 50 of the 100 cases herein reported was the Trendelenburg test done and so clearly recorded that there could be no mistake that the test was performed properly and interpreted properly. In few of these 50 cases the test was said to be negative, showing no incompetence of the valves of the internal saphenous vein, in spite of the fact that the patient had varicose veins of the calf of the leg. In 10 instances it was doubly positive, so that in 20 per cent of this group the valves of the communicating veins as well as those of the internal saphenous vein were found incompetent by the doubly positive Trendelenburg reaction. Our comparative tourniquet test was properly recorded for 56 extremities in 34 cases. In 19 instances the improvement with the tourniquet in the lower third of the thigh was greater than that with the tourniquet

at the middle or upper thirds, indicating that there was incompetence of the valves of the communicating veins; i.e., 33 per cent had incompetence of the communicating veins as well as incompetence of the valves of the long saphenous, in contrast to the 20 per cent obtained by the doubly positive Trendelenburg test. In 18 cases both tests were so performed that there was no question concerning the results obtained. The valves of the communicating veins were found incompetent in 4 (22.2 per cent) cases, both by the doubly positive Trendelenburg and our comparative tourniquet tests. In 2 additional cases, however, the valves were found to be incompetent by the latter test; whereas, the doubly positive reaction of the Trendelenburg test failed to demonstrate the incompetency. Thus, the comparative tourniquet test demonstrated

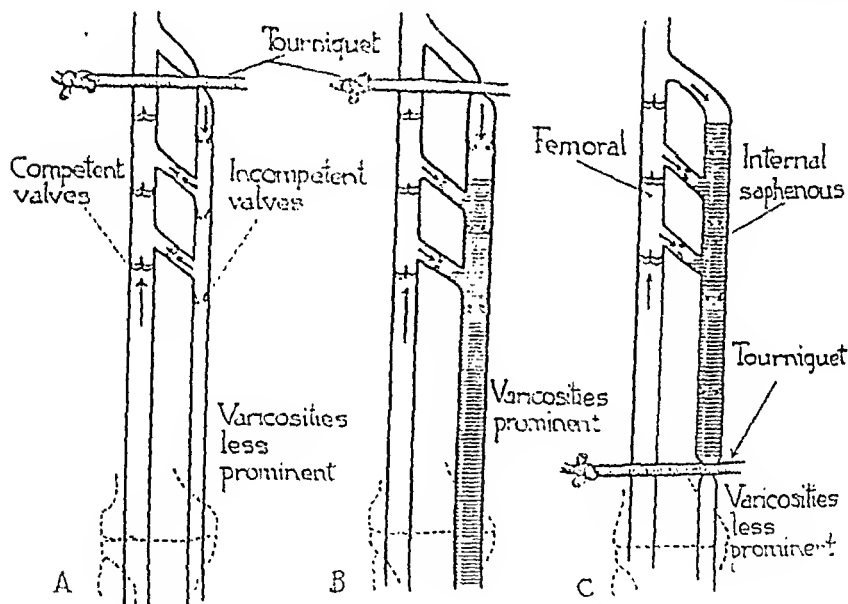


FIG. 2.—Diagrammatic illustration of the physiology involved in the comparative tourniquet test illustrated in Fig. 1. In the figure on the left (A), the tourniquet is applied at the upper third of the thigh sufficiently tight to constrict the internal saphenous vein and prevent the flow of blood through it at this level. The internal saphenous vein has incompetent valves, but the veins communicating between the deep and superficial systems have competent valves, and therefore when the patient walks with the tourniquet thus applied the varicosities below the level of the tourniquet become less prominent. The blood is pumped up the deep system and cannot spill back through the superficial system. In the second figure (B), not only are the valves of the internal saphenous system incompetent, but the valves of the veins communicating between the deep and the superficial systems are incompetent and thus the tourniquet applied in the upper third of the thigh sufficiently tight to constrict the saphenous will not stop the retrograde flow of blood through these communicating veins. Thus, the varicosities below this level when the patient walks are improved to a certain extent, but they do not entirely disappear. In the third figure (C), the tourniquet is applied in the lower third of the thigh below the lowest communicating veins with incompetent valves between the deep and superficial systems. In this instance, when the patient walks, there is further improvement over that of the second figure (B), indicating the leak through the communicating veins as well as through the main stem of the saphenous. This test shows in a statistical study that 33 per cent of the people with varicose veins have incompetent valves, not only of the internal saphenous itself, but also of the communicating veins between the deep and superficial systems. The Trendelenburg test doubly positive reaction shows incompetence of the communicating valve in only 20 per cent of a series of cases, indicating that the comparative tourniquet test is a more delicate test for estimating these additional leaks than the doubly positive Trendelenburg reaction.

incompetency of the valves of the communicating veins in 33.3 per cent; whereas, the Trendelenburg test was doubly positive in 22.2 per cent. These findings demonstrate two facts: (1) that there is a close parallelism of results obtained by the two tests, and (2) that the comparative tourniquet test is more accurate in demonstrating any leak through the communicating veins, which is of great clinical importance.

The Perthes test was recorded in 47 cases. In 46 of these, the vein below the tourniquet diminished in size when the patient walked, thus indicating indirectly that the deep veins were patent, at least at the level of the tourniquet. In 1 instance there was questionable patency of the deep veins; in other words, with the tourniquet on and the patient walking, there was no improvement and apparently a little more distention or engorgement of the superficial varicosities. From the practical standpoint with the use of the comparative tourniquet test, it is not absolutely necessary to do the Trendelenburg or the Perthes test. The comparative tourniquet test demonstrates by comparing the patient walking without the tourniquet and with the tourniquet applied at various levels whether the valves of the internal saphenous and communicating veins are incompetent, and also whether the deep veins are patent.

#### TREATMENT

When the Hutchinson Memorial Clinic of Tulane University first opened (1932), varicose veins of the lower extremities were treated entirely by the injection method. This was disappointing in some of the severe cases, because the sclerosis of the vein was not complete before other areas that had been injected were apparently recurring, and secondly, because even less severe cases in which the thrombosis of the varicosities was secured by treatment after a period of time had recurrences. We experimented with various procedures before arriving at a method which apparently gives the best results. Some of the procedures tried were simple ligation of the long saphenous vein with subsequent injection of sclerosing solutions, and ligations at various places in the thigh, low only, high only, and high and low, ligation of superficial veins, and ligations combined with the injection of sclerosing solutions at the same time the vein was sectioned and tied. Therefore, in the report of these results it is evident that there is no uniformity of procedure in many of the cases and that it is difficult to compare the results in the different groups. Not only have our clinical impressions been responsible for these changes during the development of our present therapy, but also comparative follow-up records show that in the cases treated by the presently used method the results are better and more permanent than in the other groups. Of the 100 cases, 8 deserted before any treatment of the varicose veins had been given, and 11 were transferred before any treatment was given, leaving 81 cases in which therapy was used. Seven of these 81 deserted during treatment before

at the middle or upper thirds, indicating that there was incompetence of the valves of the communicating veins; i.e., 33 per cent had incompetence of the communicating veins as well as incompetence of the valves of the long saphenous, in contrast to the 20 per cent obtained by the doubly positive Trendelenburg test. In 18 cases both tests were so performed that there was no question concerning the results obtained. The valves of the communicating veins were found incompetent in 4 (22.2 per cent) cases, both by the doubly positive Trendelenburg and our comparative tourniquet tests. In 2 additional cases, however, the valves were found to be incompetent by the latter test; whereas, the doubly positive reaction of the Trendelenburg test failed to demonstrate the incompetency. Thus, the comparative tourniquet test demonstrated

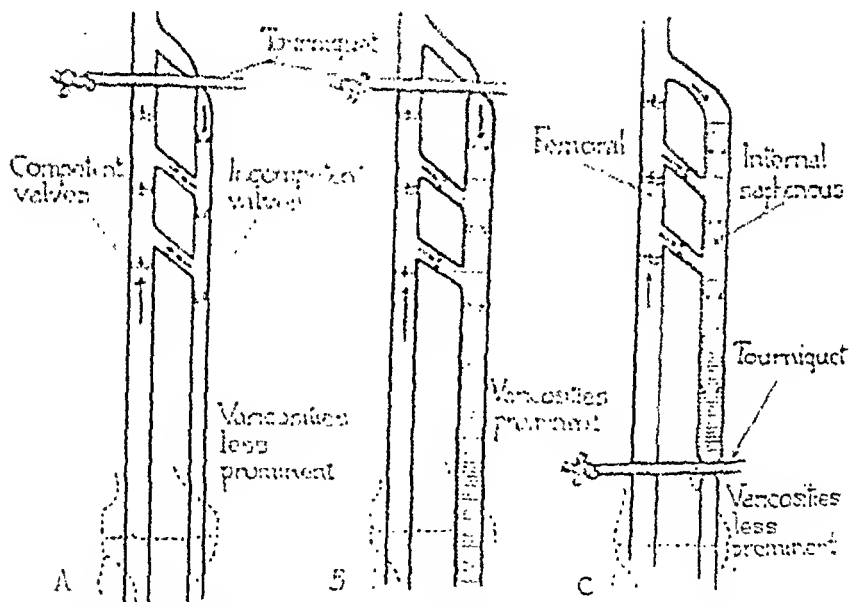


FIG. 2.—Diagrammatic illustration of the physiology involved in the comparative tourniquet test illustrated in Fig. 1. In the figure on the left (A), the tourniquet is applied at the upper third of the thigh sufficiently tight to constrict the internal saphenous vein and prevent the flow of blood through it at this level. The internal saphenous vein has incompetent valves, but the veins communicating between the deep and superficial systems have competent valves, and therefore when the patient walks with the tourniquet thus applied the varicosities below the level of the tourniquet become less prominent. The blood is pumped up the deep system and cannot spill back through the superficial system. In the second figure (B), not only are the valves of the internal saphenous system incompetent, but the valves of the veins communicating between the deep and the superficial systems are incompetent and thus the tourniquet applied in the upper third of the thigh sufficiently tight to constrict the saphenous will not stop the retrograde flow of blood through these communicating veins. Thus, the varicosities below this level when the patient walks are improved to a certain extent, but they do not entirely disappear. In the third figure (C), the tourniquet is applied in the lower third of the thigh below the lowest communicating veins with incompetent valves between the deep and superficial systems. In this instance, when the patient walks, there is further improvement over that of the second figure (B), indicating the leak through the communicating veins as well as through the main stem of the saphenous. This test shows in a statistical study that 33 per cent of the people with varicose veins have incompetent valves, not only of the internal saphenous itself, but also of the communicating veins between the deep and superficial systems. The Trendelenburg test doubly positive reaction shows incompetence of the communicating valve in only 20 per cent of a series of cases, indicating that the comparative tourniquet test is a more delicate test for estimating these additional leaks than the doubly positive Trendelenburg reaction.

their course of treatment was completed. Therefore, there is a total of 72 cases in which we can report results for comparison of the various methods. In 38 of these 72 cases, ligation and section of the vein was combined with the injected treatment. In the remaining 34, the injection treatment alone was used. In employing the injection treatment, we used sodium morrhuate 5 per cent, because it had been shown previously by us<sup>4</sup> to be more efficient as a thrombus producing agent than other substances generally used and that it is comparatively not toxic. Recently in a few instances we have used sodium gynoeardate 5 per cent and sodium soap of chaulmoogra oil, and it is our general impression that this produces a better sclerosis and more extensive thrombosis than sodium morrhuate. We have in progress some experimental work determining the value of this solution as compared to other sclerosing solutions.

In applying the injection method, we usually inject from one to three different varicosities of the patient at one time. The patient is allowed to stand and the vein is obstructed above the point of the needle just before the solution is injected. This allows the vein to collapse and the finger pressed above the point of the injecting needle permits little flow of fluid in the vein and keeps the injective solution in close contact with the intima of the vein as long as the finger compresses the vein. The compression is maintained for a minute or two, following which a compression bandage of small squares of piano felt is applied tightly over the injected area, which is removed after twenty-four hours. As a general rule, only 2 c.c. of the solution is injected in any one place, which results in thrombosis in an area varying from 2 cm. to 6 or 8 cm. From one to three varicosities are injected at one time. The patient returns at intervals of from five to seven days for repeated injections. The immediate results from this treatment have been very good, for in few instances were we unsuccessful in obtaining thrombosis completely throughout the extent of the varicose peripheral veins.

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Fig. 3.—Clinical application of the test shown in Fig. 1. The photographs were taken instantly after the patient had been walking and then stopped. In *a*, walking without a tourniquet; *b*, with tourniquet around upper third of thigh; *c*, with tourniquet around middle third of the thigh; and *d*, with tourniquet around lower third of the thigh, in each instance sufficiently tight to compress the superficial venous system. It will be noted that when the patient walks without the tourniquet the varicose veins remain prominent. When she walks with the tourniquet in the upper third of the thigh, the varicose veins though improved are not entirely gone, but when she walks with the tourniquet around the middle third of the thigh, the veins entirely disappear. Likewise, with the tourniquet around the lower third of the thigh the varicose veins are not prominent below the level of the tourniquet. The test indicates in this instance that not only is there a leak through the main opening of the saphenous, which leak is stopped by applying the tourniquet in the upper third of the thigh, but there is also a leak below this, between the upper third and the middle third, since greater improvement occurs with the tourniquet in the middle third of the thigh. Therefore, high ligation alone in this case would not cure the patient because she would have additional leaks below the main opening of the saphenous. She had high ligation and section of the vein at the upper end of the internal saphenous with injection of the distal stem, and two weeks later a ligation and section of the saphenous in the middle third of the thigh with injection of the distal stem. The lower photograph shows the patient six months after the procedure with no evidence of recurrence. The arrows indicate the scars of the operation. Ligation of the saphenous of the left leg has also been done with injection of the distal stem, but in this extremity it was necessary to ligate at only one level, as in the case of the man shown in the adjacent photograph.



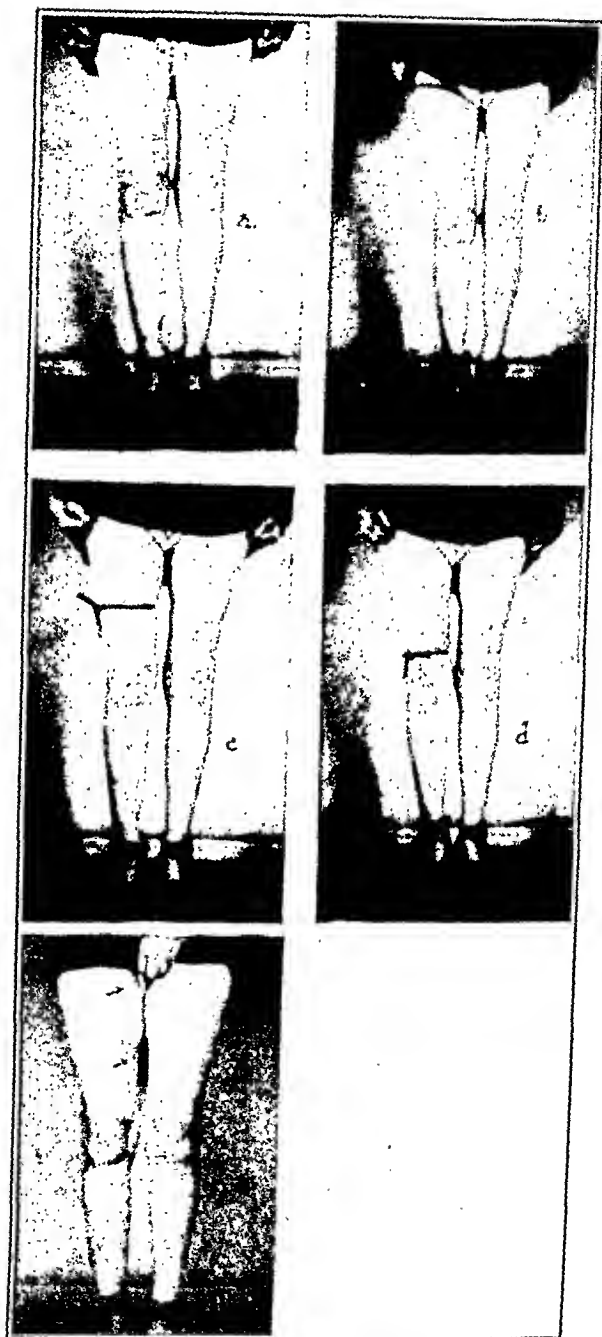


Fig. 3.—See opposite page for legend.

superficial tributary veins of the internal saphenous system) were done. This group of 14 patients in whom ligations were done below the upper end of the internal saphenous channel not combined with ligation of the internal saphenous at the fossa ovalis form an excellent group for comparison of results. We have had the same experience as Faxon,<sup>5</sup> who emphasizes so strongly that to prevent recurrence ligation must be done high on the internal saphenous. In one case the external saphenous system was ligated below the knee, and in this instance a retrograde flow through the main opening of the external saphenous vein into the popliteal vein was demonstrated by the comparative tourniquet test. This incompetency was detected by the fact that the vein did not improve when the patient walked with the tourniquet on the thigh at any of the usual three levels, but did improve when the tourniquet was placed below the knee and constricted the main stem of the external saphenous vein.

#### METHODS OF MANAGEMENT

On examination of the patient with varicose veins, if the valves of the internal saphenous system are found to be incompetent, the Trendelenburg test is positive and the comparative tourniquet test shows improvement when the patient walks with the tourniquet at the upper, middle, or lower third of the thigh, then we recommend ligation. We do not perform ligation in mild cases of varicosities or those cases in which Trendelenburg test is not positive or in which it is questionable. In mild cases of varicosities we still adhere to the injection treatment alone, and feel that if there is a great chance of recurrence the patient is at least temporarily relieved and that, if necessary, a more radical procedure in attacking the varicose veins can be performed. At the present time we feel that ligation and section of the internal saphenous system should be done high, above all of the tributaries of the internal saphenous system, because we have observed recurrences when ligation of the saphenous was performed in the middle and lower thirds of the thigh, and we believe that there is less chance for recurrence through collateral veins if the ligation is done above all collateral veins. In addition to high ligation of the internal saphenous on every extremity with moderate or severe varicosities, additional ligation and section is done below the level of the lowest communicating vein in the thigh with incompetent valves in those cases in which the comparative tourniquet test shows incompetence of the valves of the veins communicating between the deep and superficial system (Figs. 1, 2, and 3).

#### OPERATION

No special preoperative preparation of the patient is necessary. The field of the operation is prepared by shaving and by the usual skin preparation. The femoral artery is palpated at Poupart's ligament and the

## LIGATION

In 38 of the patients, section and ligation of one or more veins were performed. A total of 55 ligations were done. In 24 patients high ligations were done; i.e., at the fossa ovalis and at the upper end of the internal saphenous vein above any of its tributaries. Twenty-six extremities were operated upon in these 24 patients. In 17 of the cases only high ligation of the internal saphenous on one side was performed; whereas, in the remaining 7 cases other ligations were done in addition

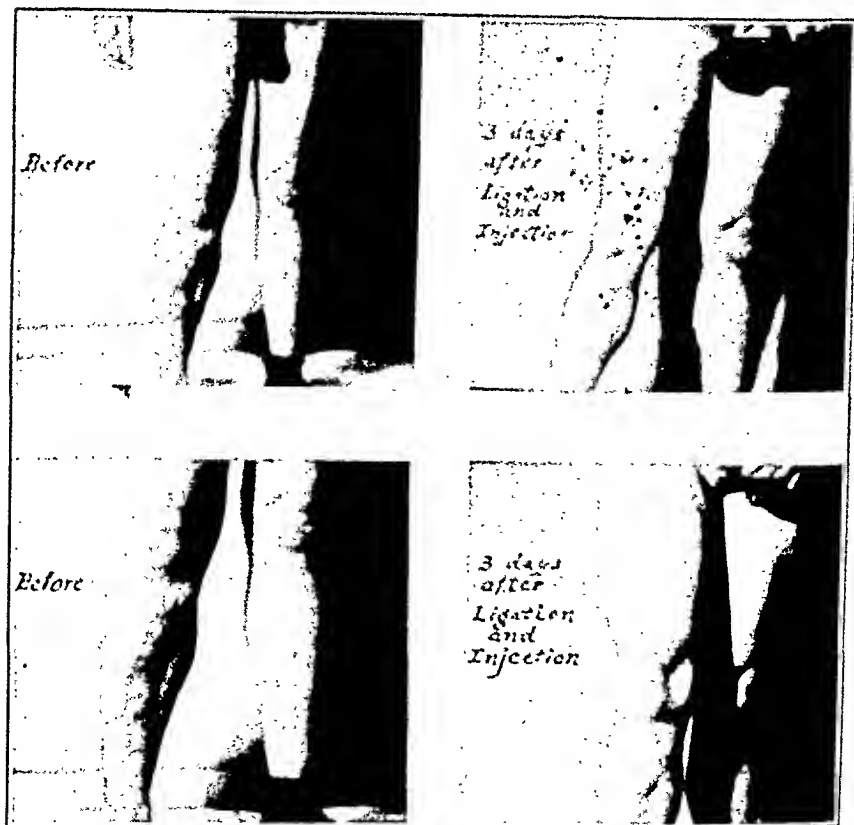


FIG. 4.—The comparative tourniquet test shown in Fig. 1 demonstrated in this patient a leak through the main stem of the saphenous with no incompetence of the valves of the veins communicating between the deep and superficial systems below the opening of the saphenous at the fossa ovalis. A single ligation and section of the upper end of the saphenous with injection of the distal stem resulted in cure. The two photographs on the left show the patient before operation and the two on the right indicate absence of varicose veins three days after the transection and ligation with injection of the distal stem. Compare with woman shown in Fig. 3, page 894.

to high ligation on one side. In 3 cases, in addition to the high ligation, the internal saphenous was also ligated in the lower third of the thigh. In 14 patients the only ligations did not include high ligation of the internal saphenous, but other operations to section and ligate veins (the internal saphenous in the middle or lower third of the thigh, or

superficial tributary veins of the internal saphenous system) were done. This group of 14 patients in whom ligations were done below the upper end of the internal saphenous channel not combined with ligation of the internal saphenous at the fossa ovalis form an excellent group for comparison of results. We have had the same experience as Faxon,<sup>5</sup> who emphasizes so strongly that to prevent recurrence ligation must be done high on the internal saphenous. In one case the external saphenous system was ligated below the knee, and in this instance a retrograde flow through the main opening of the external saphenous vein into the popliteal vein was demonstrated by the comparative tourniquet test. This incompetence was detected by the fact that the vein did not improve when the patient walked with the tourniquet on the thigh at any of the usual three levels, but did improve when the tourniquet was placed below the knee and constricted the main stem of the external saphenous vein.

#### METHODS OF MANAGEMENT

On examination of the patient with varicose veins, if the valves of the internal saphenous system are found to be incompetent, the Trendelenburg test is positive and the comparative tourniquet test shows improvement when the patient walks with the tourniquet at the upper, middle, or lower third of the thigh, then we recommend ligation. We do not perform ligation in mild cases of varicosities or those cases in which Trendelenburg test is not positive or in which it is questionable. In mild cases of varicosities we still adhere to the injection treatment alone, and feel that if there is a great chance of recurrence the patient is at least temporarily relieved and that, if necessary, a more radical procedure in attacking the varicose veins can be performed. At the present time we feel that ligation and section of the internal saphenous system should be done high, above all of the tributaries of the internal saphenous system, because we have observed recurrences when ligation of the saphenous was performed in the middle and lower thirds of the thigh, and we believe that there is less chance for recurrence through collateral veins if the ligation is done above all collateral veins. In addition to high ligation of the internal saphenous on every extremity with moderate or severe varicosities, additional ligation and section is done below the level of the lowest communicating vein in the thigh with incompetent valves in those cases in which the comparative tourniquet test shows incompetence of the valves of the veins communicating between the deep and superficial system (Figs. 1, 2, and 3).

#### OPERATION

No special preoperative preparation of the patient is necessary. The field of the operation is prepared by shaving and by the usual skin preparation. The femoral artery is palpated at Poupart's ligament and the

line of the artery may be marked with gentian violet. A longitudinal incision is made beginning 2 cm. medial to the line of the femoral artery and from 2 cm. below Poupart's ligament downward for a distance of 4 cm. After a little experience it is possible to come directly on to the internal saphenous vein near where it opens into the femoral vein at the fossa ovalis. Not infrequently the external pudendal vein will be recognized and it is necessary, as a general rule, to ligate this separately or to ligate the long saphenous above this tributary. The long saphenous is isolated and clamped with a curved hemostat and 2 c.c. of 5 per cent sodium morrhuate solution is injected into the distal segment. Another hemostat is applied just distal to the point of injection and the vein is severed between these two hemostats. The proximal stump is then transfixied and ligated, and another ligature without transfixion is put on the stump above the area of transfixion. This precautionary measure is done theoretically to prevent the propagation of a thrombus which may have originated at the cutgut transfixing the vein. Because we have had one ligature slip before the present routine of transfixing the vein, we now transfix the vein and since doing this have had no difficulty whatsoever. The inferior stump is then transfixied and ligated, but it is not necessary here to apply an additional ligature around the vein distal to the transfixion because a thrombus in the lumen of this vein is desirable. We use, as a general rule, chronic No. 1 or No. 0 catgut for this ligation. The subcutaneous tissues and skin are closed with interrupted sutures. After applying a firm dressing the patient is allowed to remain on the table for one hour. They are instructed then to go home, and to rest, either in bed or in a chair, but not to remain entirely in bed for more than a few hours at a time. Further, they are instructed to get up and to move around the room with the belief that this encourages the circulation in the deep veins of the lower extremities and helps to prevent propagation of a thrombus through the collateral veins into the deep system. We find that the majority of the superficial veins after this ligation become thrombosed soon after the operation and that the thrombus progresses downward gradually within the next few days, extending anywhere from the middle third of the thigh to the lower part of the middle of the calf of the leg. The wound is dressed on the third or the fourth day and the sutures are removed after the eighth to the tenth day. We have frequently found some induration in and around the wound in the inguinal region and have attributed this to leakage of the sodium morrhuate into the wound while injecting. In those cases where our comparative tourniquet test shows that the patient has a leak not only through the main opening of the internal saphenous vein, but also through the communicating veins from the deep to the superficial system, we ligate the internal saphenous above all its tributaries and also in the middle or lower third of the thigh, the site depending upon the results of the comparative tourniquet test. This

second ligation is done notwithstanding the fact that a thrombus may have started in the distal stump and propagated beyond this level. These thrombi disappear or wash out after a period of time if the pressure in the venous system is high. They obstruct the lumen of the vein temporarily, but the thrombus may later disappear, possibly because of abnormally high pressure arising because of incompetence of the valves of the veins communicating between the deep and superficial systems or through processes of repair. To prevent this regeneration, secondary ligation of the stem of the internal saphenous is done in the middle or lower third of the thigh below the lowest communicating vein between the deep and superficial systems of the thigh with incompetent valves, as demonstrated by our test, from ten days to three weeks after the first ligation. Other secondary ligations may be done for marked varicosities in collateral channels and these are frequently found on the anterior surface of the thigh subcutaneously, a vein tributary to the external circumflex iliae or internal saphenous, i.e., the external superficial femoral. Additional ligations may be made posteriorly on the thigh, channels running from the gluteal veins or veins in the gluteal region. Independent ligation of these trunks is frequently necessary and at the time of ligation injection of sodium morrhuate is made into the distal stump. Varicose veins in these regions have a peripheral retrograde flow and the ligation should be made at the highest level to produce obliteration of the entire vein. Occasionally posteriorly on the lower third of the thigh varicose channels are found in which the flow is toward the external saphenous system. If ligation is indicated here, on theoretical grounds it should be done low on the varicosity and the vein injected above the point of section to prevent a thrombus from entering the popliteal vein. In rare instances we have found that the external saphenous system itself was varicosed, not by virtue of the connections with the internal saphenous system, but because of incompetent valves in the main stem of the former, which opens into the popliteal. This is diagnosed by the comparative tourniquet test. When the veins of the calf which comprise the external saphenous system do not collapse when the tourniquet is placed even at the lower third of the thigh and the patient walks, but do disappear when the tourniquet is placed immediately below the knee, it is evident that the varicosities of the calf neither are due to a direct leak through the communicating veins from the deep to the superficial system in the calf nor are from a retrograde flow from the internal saphenous system in the thigh, but are the result of incompetence of valves of the external saphenous system. If the varicosities were due to leaks through the communicating veins between the deep and superficial systems in the calf, there would be no improvement even when the tourniquet is placed below the knee. Ligation and section and simultaneous injection of sclerosing solution do not take care of all of the varicose veins in every instance. Occa-

line of the artery may be marked with gentian violet. A longitudinal incision is made beginning 2 cm. medial to the line of the femoral artery and from 2 cm. below Poupart's ligament downward for a distance of 4 cm. After a little experience it is possible to come directly on to the internal saphenous vein near where it opens into the femoral vein at the fossa ovalis. Not infrequently the external pudendal vein will be recognized and it is necessary, as a general rule, to ligate this separately or to ligate the long saphenous above this tributary. The long saphenous is isolated and clamped with a curved hemostat and 2 c.c. of 5 per cent sodium morrhuate solution is injected into the distal segment. Another hemostat is applied just distal to the point of injection and the vein is severed between these two hemostats. The proximal stump is then transfixied and ligated, and another ligature without transfixion is put on the stump above the area of transfixion. This precautionary measure is done theoretically to prevent the propagation of a thrombus which may have originated at the catgut transfixing the vein. Because we have had one ligature slip before the present routine of transfixing the vein, we now transfix the vein and since doing this have had no difficulty whatsoever. The inferior stump is then transfixied and ligated, but it is not necessary here to apply an additional ligature around the vein distal to the transfixion because a thrombus in the lumen of this vein is desirable. We use, as a general rule, chronic No. 1 or No. 0 catgut for this ligation. The subcutaneous tissues and skin are closed with interrupted sutures. After applying a firm dressing the patient is allowed to remain on the table for one hour. They are instructed then to go home, and to rest, either in bed or in a chair, but not to remain entirely in bed for more than a few hours at a time. Further, they are instructed to get up and to move around the room with the belief that this encourages the circulation in the deep veins of the lower extremities and helps to prevent propagation of a thrombus through the collateral veins into the deep system. We find that the majority of the superficial veins after this ligation become thrombosed soon after the operation and that the thrombus progresses downward gradually within the next few days, extending anywhere from the middle third of the thigh to the lower part of the middle of the calf of the leg. The wound is dressed on the third or the fourth day and the sutures are removed after the eighth to the tenth day. We have frequently found some induration in and around the wound in the inguinal region and have attributed this to leakage of the sodium morrhuate into the wound while injecting. In those cases where our comparative tourniquet test shows that the patient has a leak not only through the main opening of the internal saphenous vein, but also through the communicating veins from the deep to the superficial system, we ligate the internal saphenous above all its tributaries and also in the middle or lower third of the thigh, the site depending upon the results of the comparative tourniquet test. This

order to excise badly scarred ulcer base and to perform skin grafts. In 3 instances Davis grafts alone were done; in 1 of these it was repeated. In 2 instances Wolfe-Kraus as well as Davis grafts were used. In spite of the fact that in every instance the ulcer healed, they did not all remain healed. In 3 cases ulcers broke down one or more times. It has been our experience that ulcers of the leg due to varicose veins, as a general rule, occur in dirty, indolent, indifferent, careless patients. These characteristics predispose to a recurrence and we have begun to regard the bad leg ulcer as almost hopeless for a permanent cure, and a lifelong charge on the institution. It is not so much the pathology as the indolence of the patients who repeatedly provide an activating cause which prompts the expression of this note of discouragement in these cases.

### RESULTS

It was possible to reexamine 25 patients who had finished the injection treatment with no operative procedure from six months to three and one-half years previously. Twenty patients who had been treated by ligation and injection at one or more levels from six months to eighteen months previously were reexamined. Of those treated by injection method alone, there were 40 extremities in the 25 patients, 15 patients receiving treatment in both lower extremities. There was recurrence of varicosities in 23 (57.5 per cent), no recurrence in 17 (42.5 per cent). In fairness to the method, it was noted by us as by others that the subjective results were better than the objective; i.e., a patient may feel that the varicose veins have remained well, although there are definite varicosities present. In general, the patients feel more comfortable and do not feel fatigue in the extremities as quickly, and other symptoms have not returned with the same intensity as when originally present. It may be that the pressure in these varicosities is less and that partial thrombosis above these areas has diminished to some extent the volume and rapidity of back flow in the internal saphenous system. Five of the 25 patients who had ligations at one or more levels of the internal saphenous system had ligations in both lower extremities. There were 25 extremities in which reexamination was possible from six months to two and one-half years after the procedure. Eleven of the extremities had ligations only at the upper end of the internal saphenous vein with simultaneous injection of a sclerosing solution. Two of these recurred (18 per cent), 9 (82 per cent) remained well (in contrast to 42.5 per cent with the injection treatment). Of 12 ligations of the internal saphenous in the middle or lower third of the thigh without ligation of the same saphenous at the upper end, 6 had recurrence of varicosities (50 per cent), and 6 (50 per cent) remained well. Only 2 cases were reexamined where high and low ligations were performed on the same saphenous vein. One of these had recurrence, but 2 is too few for comparison.



sionally, a few varicosities remain on the calf or the thigh which should be injected with sclerosing solutions. We find that after ligation the tension or pressure in the vein itself is greatly reduced and that it is easier to produce thrombosis and the incidence of recurrence is diminished.

#### ULCERS

The presence of varicose ulcers changes the treatment routine for varicose veins. Of the cases in our series, 29 had varicose ulcers. Twenty-one of these were females and 8 were males. This incidence of 29 per cent ulcers is a very good indication of the severity of the cases. Many of these varicose ulcers were long standing and large. Some had been present for as long as twenty years. The youngest male with a varicose ulcer was 33 years of age and the oldest male was 72. The average age of the males with varicose ulcer was 50.4 years. The youngest female was 32 years of age and the oldest female was aged 70 years. The average age of the females with varicose ulcers was  $49\frac{1}{3}$  years. Veins are not ligated in the presence of an infected ulcer. The ulcer must be treated conservatively and must be entirely healed and free of infection before ligation is attempted. Though we have ligated a few veins in the presence of ulcers which were almost healed, we believe that ligation in the presence of infection below is not without danger because of the possibility of propagation of the infection. In our series, we have had no operative fatalities and no emboli, either fatal or merely small infarctions of the lungs. The treatment of the ulcer depended upon its type and appearance when the patient was first seen. If it was acutely inflamed or badly infected, the patient was treated with bed rest, elevation of the involved extremity, and application of "hypertonic" saline dressings. When the acute infection subsided and healthy granulation tissue began to appear, the ulcer was treated by compression dressings or an Unna's paste boot. In cases in which compression was used, sterile xeroform gauze (5 per cent xeroform in white vaseline) was applied directly to the ulcer, and this was covered with sterile plain gauze and fixed in position with adhesive plaster. A moist marine sponge (sterilized by immersing for one week in  $\frac{1}{1000}$  bichloride solution and washed thoroughly with sterile water) is then applied to the covered ulcer and firmly compressed against it by applying a snug circular bandage. Occasionally a rubber bath sponge was used instead of a marine sponge, but we found that the marine sponge gave a more even compression. The patient returned every three to five days for renewal of the dressing. Unna's paste boot was found even more effective in some cases. Care should be taken to see that it is properly applied, and it can remain on for from ten days to three weeks. It was not always possible to promote healing by these conservative methods. Five patients were referred to Neal Owens, in charge of the Plastic Surgery Department. All of these were hospitalized in

order to excise badly scarred ulcer base and to perform skin grafts. In 3 instances Davis grafts alone were done; in 1 of these it was repeated. In 2 instances Wolfe-Kraus as well as Davis grafts were used. In spite of the fact that in every instance the ulcer healed, they did not all remain healed. In 3 cases ulcers broke down one or more times. It has been our experience that ulcers of the leg due to varicose veins, as a general rule, occur in dirty, indolent, indifferent, careless patients. These characteristics predispose to a recurrence and we have begun to regard the bad leg ulcer as almost hopeless for a permanent cure, and a lifelong charge on the institution. It is not so much the pathology as the indolence of the patients who repeatedly provide an activating cause which prompts the expression of this note of discouragement in these cases.

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## SUMMARY

Of 247 cases of varicose veins, approximately 60 per cent were in pregnant females.

Pregnancy and heredity are both important etiologic factors in the development of varicosities.

An accurate knowledge of competency of the valves in the superficial and communicating veins is essential to determine the type of therapy to be used in varicosities, and also for prognostication.

The comparative tourniquet test previously described by us is the most sensitive and most accurate test for determining incompetency of the valves of the veins communicating between the deep and superficial veins, and therefore the most important for determining the type of therapy.

Injection of sclerosing solution alone in the treatment of varicose veins resulted in recurrence in 57.5 per cent of instances; whereas, high ligation and section of the saphenous with simultaneous injection of sclerosing solution resulted in recurrence in only 18 per cent of instances.

The physiologic reasons are stated why it is essential to ligate low as well as high in the cases where the comparative tourniquet test demonstrates incompetence of the valves of the veins communicating between the main deep veins and the superficial systems.

Varicose ulcers are treated conservatively before radical measures to cure the varicosities are instituted.

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## VARICOSE VEINS TREATED BY COMBINED LIGATION AND INJECTION

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THE present popular method of treating varicose veins by the injection of sclerosing solutions appeals to both the physician and the patient in that it is simple and safe, inexpensive, and ambulatory. Experience has taught, however, that when employed alone the method is followed by frequent recurrences, even greater than those following the older operations of ligation, stripping, and excision. To avoid these recurrences and to facilitate primary obliteration by injections, several ligation procedures are now employed as adjuncts to the injection method.

When one recalls that varicose veins were ligated as early as the seventh century, that an injection method was used as early as 1858, and that even ligations and injections were combined in 1904, the progress in the therapy of varicose veins seems hardly remarkable. Nevertheless, improvement in the solutions used for injections and a better understanding of the principles of ligation have made modern treatment highly satisfactory. Thus, the older toxic coagulants used for injections have been replaced by nontoxic sclerosing solutions and the point of saphenous ligation has been progressively advanced upward to reach finally the femoral junction itself, above all the saphenous tributaries.

No attempt will be made to review the vast amount of literature, that has accumulated on the treatment of varicose veins. An exhaustive historical review may be found in E. Edwards<sup>1</sup> article in *Surgery, Gynecology and Obstetrics* for December, 1934. Articles by De Takats,<sup>2</sup> Homans,<sup>3</sup> Faxon,<sup>4</sup> Ferguson,<sup>5</sup> and the paper of E. Edwards referred to above are pertinent to the thesis of this paper, "The Treatment of Varicose Veins." Early in the return to popularity of the injection method, De Takats advocated ligation of the saphenous high in the upper thigh preliminary to injections, whenever the saphenous was very dilated. He claimed by this procedure to prevent embolism and to increase the ease of subsequent sclerosis by injection due to a reduction in downward venous pressure. A third and by far more important indication for some ligation procedure, accessory to the injection method, soon became apparent as the percentage of recurrence following the injection method alone was found to be much greater than originally reported. These recur-

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Received for publication, May 27, 1937.

rences were attributed chiefly to recanalization of the veins from excessive downward venous pressure and an associated ligation procedure could be expected to correct the trouble. When, however, the ligation was performed high in the thigh after the manner of De Takats, recurrences were still frequent, due to elongation of the saphenous stump left by the operation, or to dilatations of the tributary veins above the ligation site. Faxon, Edwards, the writer, and others following Homan's suggestion raised the ligation site to the very femorosaphenous junction, ligating the vein flush with the femoral and dividing the branches encountered at this point. With the recanalizing influence of the downward venous pressure eliminated, with tributaries which might

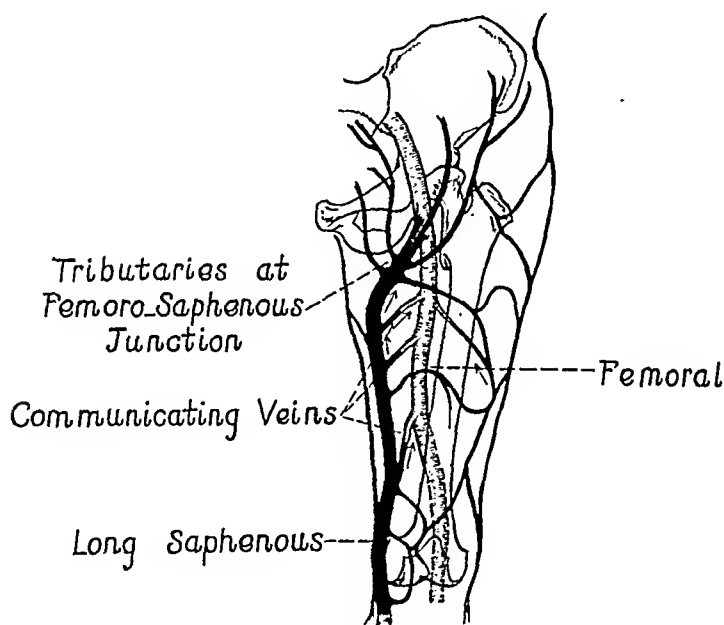


Fig. 1.—Relationship of long saphenous to deep venous system.

form collateral circulation interrupted, and without a stump which might elongate, the results of the injection method could be expected to be much better. Statistics are rapidly accumulating to indicate this to be the case. However, high ligation and injection, alone, often do not prove adequate for "blow-out" of the long saphenous in the mid or lower thigh. The explanation for this is given later, but suffice it to say now that such cases require multiple ligation procedures as described by Ferguson,<sup>5</sup> each case being individualized and ligation procedures performed at the femorosaphenous junction or at any other indicated "blow-out" sites.

In the combined method of treating varicose veins, injections are made through the opened vein at the time of the ligation or subse-

quently by the usual technique, according to individual preference. The stages in the change of modern conception of the treatment may be summarized as follows:

1. Revival of the old injection method employing nontoxic sclerosing solutions instead of toxic coagulants.
2. Revival of ligation preliminary to injection.
3. Advance upward of the ligation site to the femorosaphenous junction with division of all tributaries at this point. Simultaneous or subsequent injection of the distal segment.
4. Ligation of all "blow-out" points with simultaneous or subsequent injections.

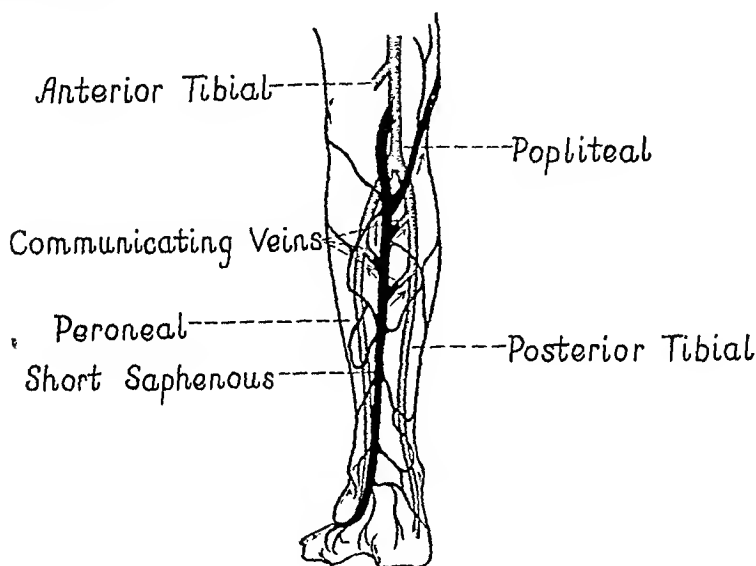


Fig. 2.—Relationship of short saphenous to deep venous system.

5. Controlled injections, the extent of the inflammation being limited by a secondary lower vein ligation.

Experience rapidly taught me, as it did others, that no two cases are alike, and that a procedure indicated for one would be of no value or would even be contraindicated for another. In general, I employ the injection method alone for simple cases with a negative Trendelenburg test, and radically high ligation and simultaneous injection, whenever the saphenous is dilated high in the thigh and whenever Trendelenburg's test is positive. Separate ligations with or without simultaneous injections are also made at all "blow-out" points lower in the leg. In addition, whenever indicated, I have limited the segment of vein affected by the sclerosing solution by injecting between two ligated points. I will try as briefly as possible to describe the principles and technique employed.

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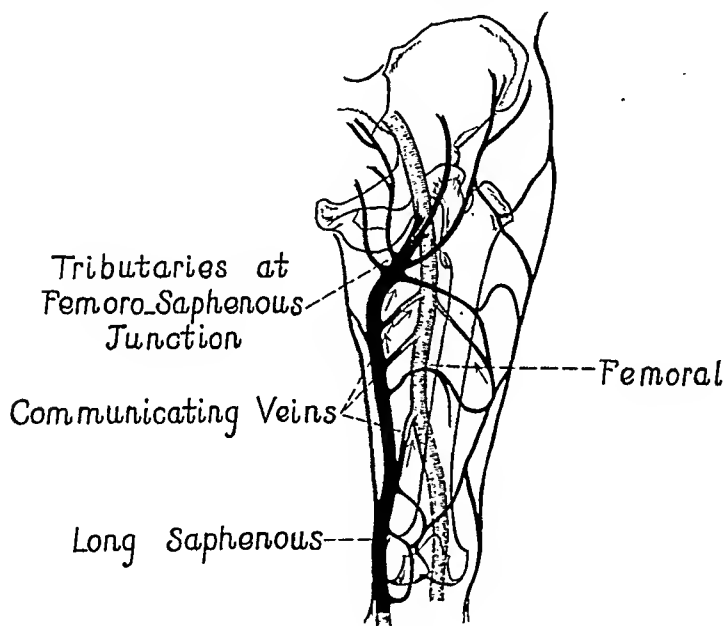


Fig. 1.—Relationship of long saphenous to deep venous system.

form collateral circulation interrupted, and without a stump which might elongate, the results of the injection method could be expected to be much better. Statistics are rapidly accumulating to indicate this to be the case. However, high ligation and injection, alone, often do not prove adequate for "blow-out" of the long saphenous in the mid or lower thigh. The explanation for this is given later, but suffice it to say now that such cases require multiple ligation procedures as described by Ferguson,<sup>5</sup> each case being individualized and ligation procedures performed at the femorosaphenous junction or at any other indicated "blow-out" sites.

In the combined method of treating varicose veins, injections are made through the opened vein at the time of the ligation or subse-

3. The veins of the superficial system, all branches of the long and short saphenous, are relatively poorly supported by soft parts and readily dilate to become varicose. The short saphenous passes under

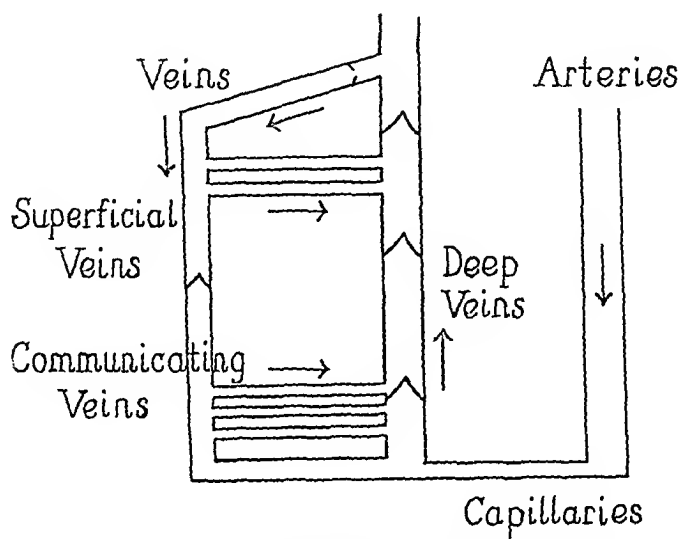


Fig. 4.—Venous circulation in varicose state. Trendelenburg test may or may not be positive.

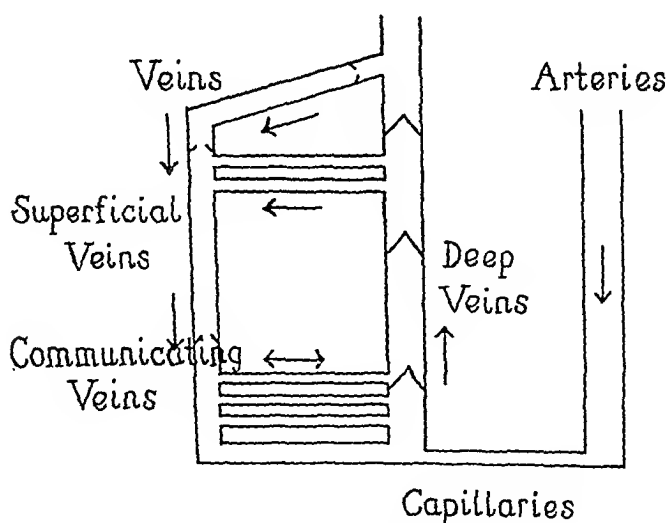


Fig. 5.—Venous circulation in varicose state, communicating veins incompetent and Trendelenburg test often doubly positive.

the deep fascia for several inches before entering the popliteal, and this fascial support makes it somewhat less prone to give away than the long saphenous.

4. The short and long saphenous are connected by a branch on the inner side of the leg above the knee. Thus a "give-away" of the long saphenous may lead to varicose formation in the short saphenous.



Although throughout this paper emphasis is placed on the combination of ligation and injection, it is not to be inferred that ligation is an invariable adjunct to the injection method. A large percentage of cases is still handled by injections alone. Even some large varicosities respond to the simple injection as long as they are not in intimate connection with an incompetent saphenous trunk or an incompetent communicating vein.

#### NORMAL ANATOMY

Large arteries carry a more or less constant supply of blood to the lower extremity to be returned from the leg by two systems of veins, a deep system accompanying the principal arteries, and a superficial system having no arterial analogue. This superficial venous system is

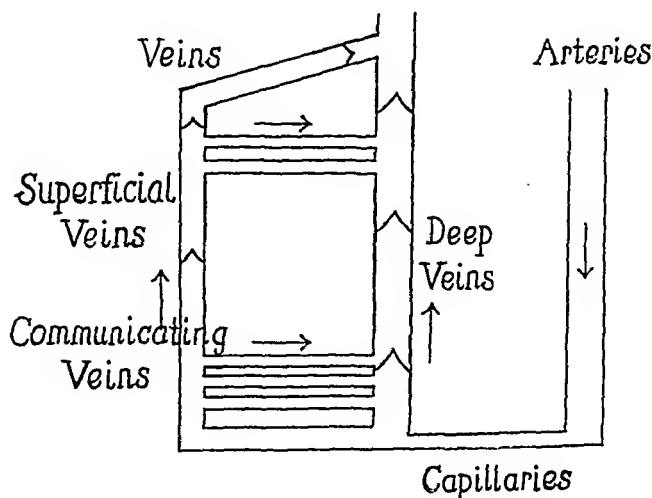


Fig. 3.—Normal venous circulation.

apparently not indispensable, as suggested by the lack of dire consequences when a considerable portion of it is destroyed in the treatment of its chief disease, varicosity. The following characteristics of the venous systems of the lower extremity are important in our discussion.

1. The veins of the superficial system are connected by important communicating veins with the deep system. The communications are frequent in the lower leg, especially about the ankle, calf, and knee. In the thigh there are at least two important communications in addition to the femorosaphenous junction, one about one-third way up and the other about one-half way up the thigh.

2. The veins of both systems are supplied with valves with cusps arranged to maintain the upward position reached by the column of blood. The valves of the communicating veins normally allow the blood to flow from the superficial to the deep veins.

Should the case present dilatation of the long saphenous lower than the femorosaphenous junction, the suspected "blow-out" site is tested by a modification of the Trendelenburg test. The extremity is raised and the finger used to compress the uppermost part of the dilated vein. Still compressing the vein, the leg is lowered. A reflux of blood downward as the finger is removed indicates incompetency of the vein valve at this point with probable competency of the valves above. Such

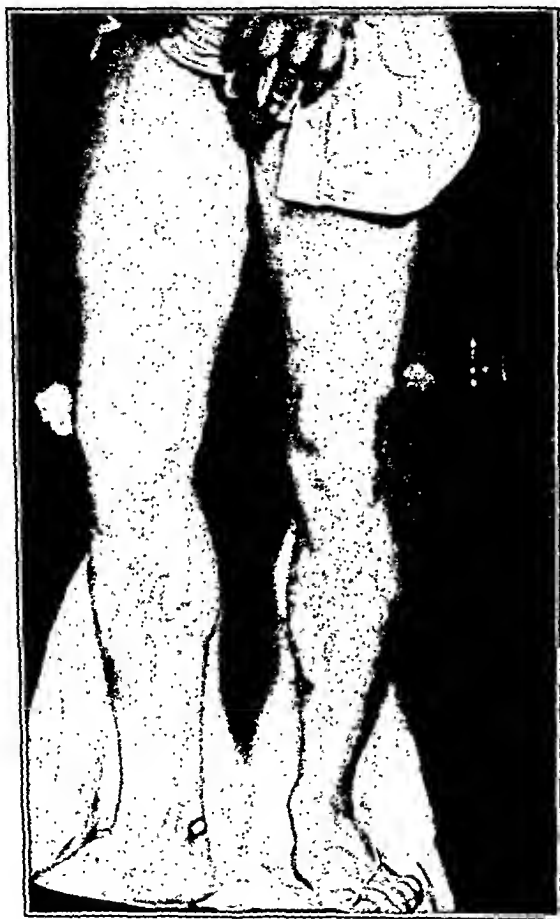


Fig. 6.—Infra-red photograph of a case of varicose veins.

"blow-out" points occur often in the mid thigh, lower third of the upper leg, and at the knee level. "Blow-outs" at these points require simple ligation and division of the vein at the "blow-out" level followed by the injection of the related varicosities. The operation will be above the highest incompetent valve and below the lowest competent one. Ligation higher in the groin at the femorosaphenous junction will fail entirely here, as can be demonstrated by performing Trendelenburg's test with the tourniquet in the groin in the usual fashion.

## THE VARICOSE STATE

The veins of the superficial system, possibly hereditarily predisposed, readily enlarge when subjected to factors of pressure, obstruction, injury, hormonal influence, or infection. Associated with the dilatation is an incompetent condition of the vein valves so that the flow of blood is retrograde in the upright position. Blood passes down instead of up the short or long saphenous, then through the communicating veins of the lower leg into the deep system and up through the popliteal and femoral to the thigh. There is then usually a spill over into the long saphenous again, due to the incompetency of the valve at the femorosaphenous junction. Further, this varicose state may involve the communicating veins, so that the blood may pass abnormally from the deep to the superficial veins at one or more points in the leg in addition to the spill over at the femorosaphenous junction.

## EXAMINATION OF THE PATIENT AND PLAN OF TREATMENT

After the routine physical examination has been made, the patient is asked to stand up before a good light for accurate study of his varicose condition. Often a plain or infra-red photograph is taken for "before and after records." Inspection and palpation are then employed to locate the main varicose trunks, and the uppermost point of enlargement of these trunks is recorded as the "give-away" or "blow-out" site. If the varicosities are small, no special tests are performed. Such cases require simple injections only. Some of my experiences with the injection method alone are described in previous articles.<sup>6,7</sup> It is well to remember that even these small veins have a tendency to recur and the patient should return at stated intervals for a considerable time for observation.

We are concerned in this paper principally with large varicose veins or cases of recurrence following previous injection or operative attempts at cure. The long saphenous may or may not be visibly dilated in the thigh, but the intelligent use of the tourniquet, bearing in mind Trendelenburg's principles, will always demonstrate the nature of the pathology present.

A positive Trendelenburg test with the tourniquet applied high in the groin demonstrates a "spill-over" from the deep to the superficial system at the femorosaphenous point and at once indicates that the case should be ligated, as well as injected, at this site, if rapid recanalization and recurrence are to be avoided. Often the test will be positive with respect to varicosities in the lower leg even though the long saphenous does not seem to be dilated on inspection or palpation. It is important to bear this in mind in the obese, in whom an unsuspected incompetent long saphenous is the chief cause of therapeutic failure.

Should the case present dilatation of the long saphenous lower than the femorosaphenous junction, the suspected "blow-out" site is tested by a modification of the Trendelenburg test. The extremity is raised and the finger used to compress the uppermost part of the dilated vein. Still compressing the vein, the leg is lowered. A reflux of blood downward as the finger is removed indicates incompetency of the vein valve at this point with probable competency of the valves above. Such

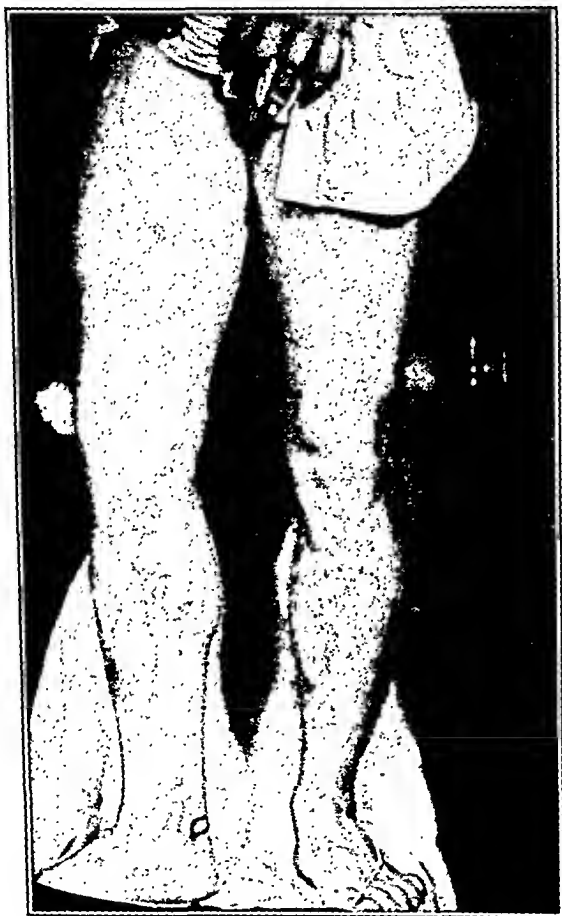


Fig. 6.—Infra-red photograph of a case of varicose veins.

"blow-out" points occur often in the mid thigh, lower third of the upper leg, and at the knee level. "Blow-outs" at these points require simple ligation and division of the vein at the "blow-out" level followed by the injection of the related varicosities. The operation will be above the highest incompetent valve and below the lowest competent one. Ligation higher in the groin at the femorosaphenous junction will fail entirely here, as can be demonstrated by performing Trendelenburg's test with the tourniquet in the groin in the usual fashion.

Cases are also encountered which present a "blow-out" in the mid or lower thigh as well as some incompetency at the femorosaphenous point. Operation here requires a double procedure, high ligation and injection at the femorosaphenous junction and separate ligation of the lower "blow-out" point.

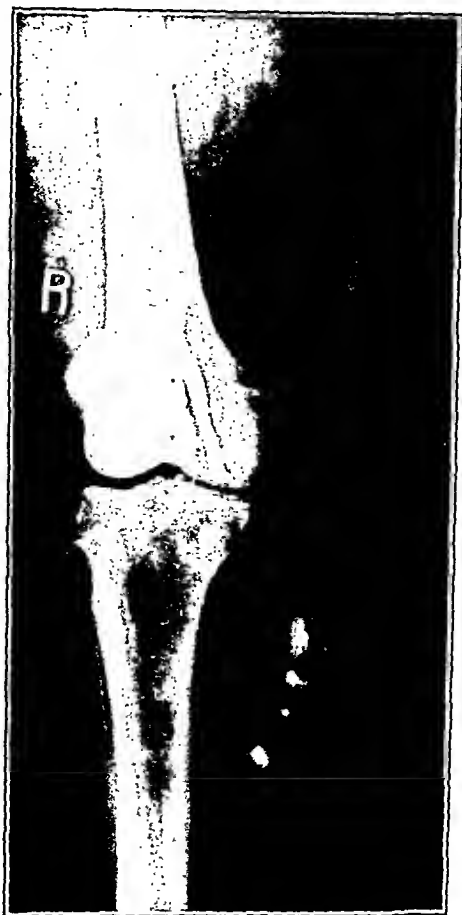


FIG. 7.—A radiograph with hippuran demonstrating an unsuspected incompetent long saphenous. Visible varices only in lower leg.

Varicosities of the calf and lateral aspect of the leg require careful inspection and palpation of the short saphenous, as a "blow-out" may exist which requires ligation and division in the popliteal space. Ligation of the long saphenous at any point in the leg cannot be expected to influence varicosities of this vein, which joins the femoral directly in the popliteal triangle.

Having decided upon the "blow-out" sites, I then usually study the venous tree below this point to decide how extensive the inflammatory

reaction is apt to be if the proximal end of the vein is injected at the time of ligation. Usually a second point for ligation is chosen to limit this reaction as discussed later.

I lay little emphasis on the test for patency of the deep veins, although this must of course be known before any method of treating varicose veins is adopted. This matter may be summarized as follows:



Fig. 8.—Radiograph with hippuran. The Trendelenburg test is doubly positive. A long vein communicating with the deep and superficial system is seen.

1. Deep Veins Patent.—No past history of “milk leg”; no edema of leg; tight elastic stocking worn with comfort; negative Perthes test.

2. Deep Veins Occluded.—Compensatory enlargement of veins across lower abdomen; persistent leg edema and leg fibrosis; positive Perthes test; past history of “milk leg.”

The examination of the patient is not complete unless the relation of all the varicosities to the main venous trunk has been determined. Often, percussing a varix, while palpating the main trunk above it,

will demonstrate their relationship. In very puzzling cases, x-ray visualization of the varicosities, after the injection of hippuran, is of value. Undiluted hippuran when injected into a varicosity for x-ray visualization frequently thromboses the veins. This simply lessens the number of injections the patient will need subsequently, but it is well to advise the patient what it to be expected. The procedure should not be used if the deep veins are occluded.



FIG. 9.—Radiograph with hippuran. A case showing secondary "blow-out" point below knee. Accessory branches are seen to be the cause of secondary dilatation.

#### INDICATIONS FOR COMBINED LIGATION AND INJECTION

1. All positive Trendelenburg cases. The operation is performed at the femorosaphenous junction. Often the saphenous is also divided just above the knee to limit the inflammatory reaction from injection.
2. All cases with well-defined "blow-out" sites lower in leg. The operation is done in mid thigh, lower thigh, or wherever the "blow-out" occurs.

3. Varicosities of the short saphenous require ligation in the popliteal space.

4. Cases presenting a doubly positive Trendelenburg theoretically demand division of all communicating veins as well as femorosaphenous ligation and injection. Practically it often suffices to ligate and

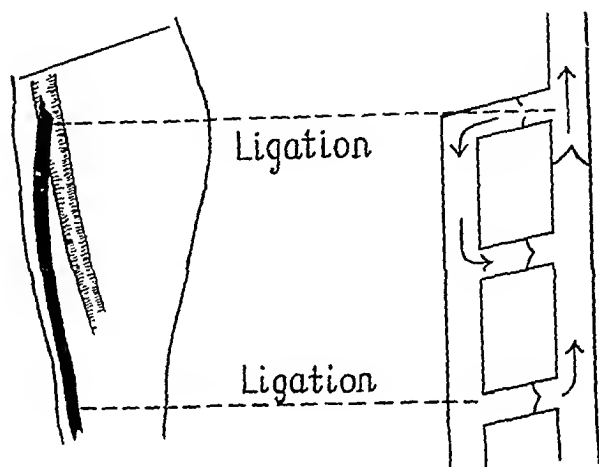


Fig. 10.—Diagrammatic illustration of cases requiring ligation. All cases presenting a positive Trendelenburg. Ligation and injection at femorosaphenous junction. Secondary ligation lower in leg to limit inflammatory reaction from injection.

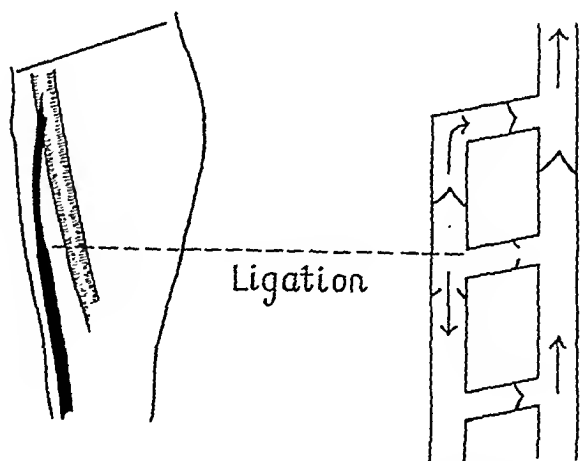


Fig. 11.—Diagrammatic illustration of cases requiring ligation. Cases presenting "blow-outs" below femorosaphenous site. Figures illustrate ligation of "blow-out" in mid thigh, above incompetent valve and below last competent valve.

inject at the femorosaphenous point and at each "blow-out" site lower in the leg, dividing communicating veins encountered in the operative areas. In persistent cases the operation recently described by Faxon<sup>8</sup> may be performed. The deep fascia is incised extensively and the communicating veins divided as the fascial flaps are dissected back.



5. Cases exhibiting a positive Trendelenburg and a secondary "blow-out" site lower in the leg. In addition to ligation and injection at the femorosaphenous junction, another ligation lower in the leg at the secondary "blow-out" site is required.

*Contraindications to Combined Ligation and Injection.*—These are relatively few. Persistent occlusion of the deep veins constitutes a definite contraindication. Nephritis, hyperthyroidism, cardiac disease may make the procedure inadvisable. Pregnancy is not a contraindication. To the contrary, high ligation influences favorably even varicosities of the vulva in pregnancy.

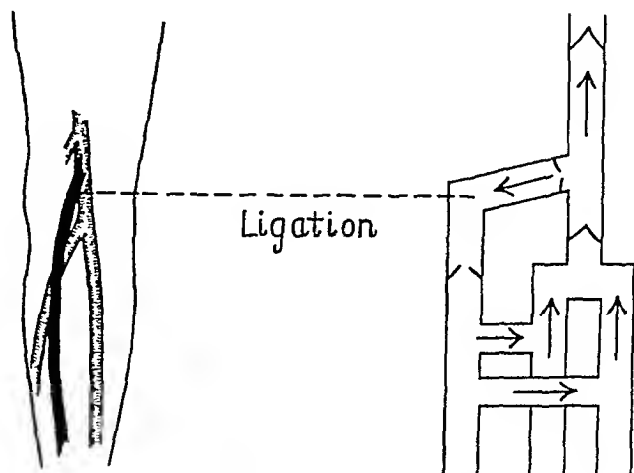


Fig. 12.—Diagrammatic illustration of cases requiring ligation. "Blow-out" of short saphenous. Ligation in popliteal space.

#### THE TECHNIQUE OF LIGATION OF "BLOW-OUT" BELOW THE FEMOROSAPHEOUS JUNCTION

This is a simple office procedure. The site of the proposed incision is marked with the patient standing. Aeriflavine, 4 per cent, followed by tincture of iodine is used for this purpose, a black cross resulting. With the patient recumbent, the operative field is further painted with tincture of iodine, preserving the black cross of the proposed incision. The area is infiltrated with 1 per cent novocaine and the vein is cut down upon, through a transverse incision about  $1\frac{1}{2}$  inches wide. Even in the lower thigh and leg, the saphenous is under the superficial fascia which must be divided. It is important not to mistake a small superficial branch for the larger vein under the fascia. Several centimeters of the vein are resected, the distal end being injected with sodium morrhuate solution, if desired, after the manner described below under femorosaphenous ligation. Any collateral veins in the field of operation are divided. A careful search is made for a communicating vein to the deep system and same divided if found. Interrupted

sutures are used to obliterate the dead space and the skin closed with dermal. An Ace leg bandage is used to bind the leg and hold the dressing in place. The patient is allowed to get up at once and provided with a few codeine tablets for pain. He is encouraged to resume his daily routine. At subsequent visits, the varicosities, which have not spontaneously thrombosed following the ligation, are injected in the usual manner.

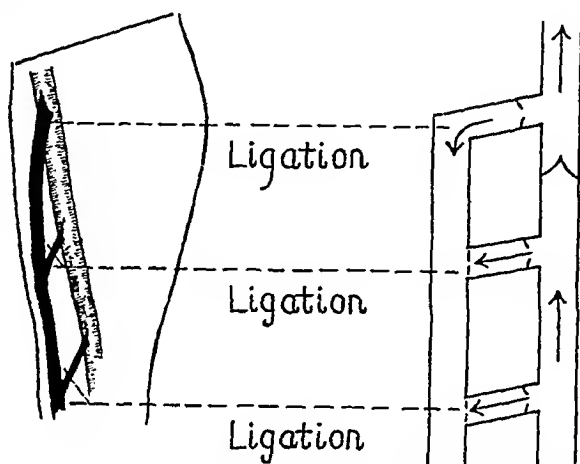


Fig. 13.—Diagrammatic illustration of cases requiring ligation. Cases exhibiting a doubly positive Trendelenburg require ligation at femorosaphenous junction and all communicating veins lower in leg.

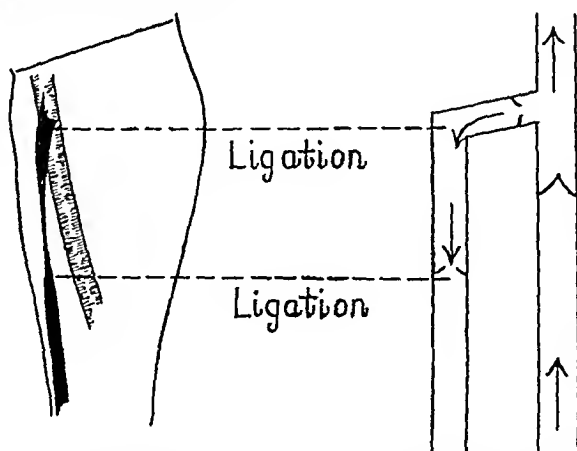


Fig. 14.—Cases exhibiting a positive Trendelenburg and a secondary "blow-out" lower in leg. In addition to ligation and injection at femorosaphenous junction another ligation lower in leg at secondary "blow-out site is required.

#### THE TECHNIQUE OF LIGATION AND SIMULTANEOUS INJECTION OF THE SAPHENOUS AT THE FEMOROSAPHENOUS JUNCTION

This is a somewhat more formidable procedure when properly done and is best performed in the hospital operating room. The landmarks are the spine of the symphysis and the pulsating femoral artery. The

femorosaphenous junction is about 1.7 cm. below the level of the spine of the symphysis as shown by Edwards<sup>1</sup> in numerous dissections. I make a transverse incision extending from the femoral pulsation mesialward, about 1 cm. below the presumed site of the femorosaphenous junction, or about 3 cm. below the level of the spine of the symphysis, thus approaching the vein a little below the femorosaphenous point. To operate directly over the junction is needlessly confusing.

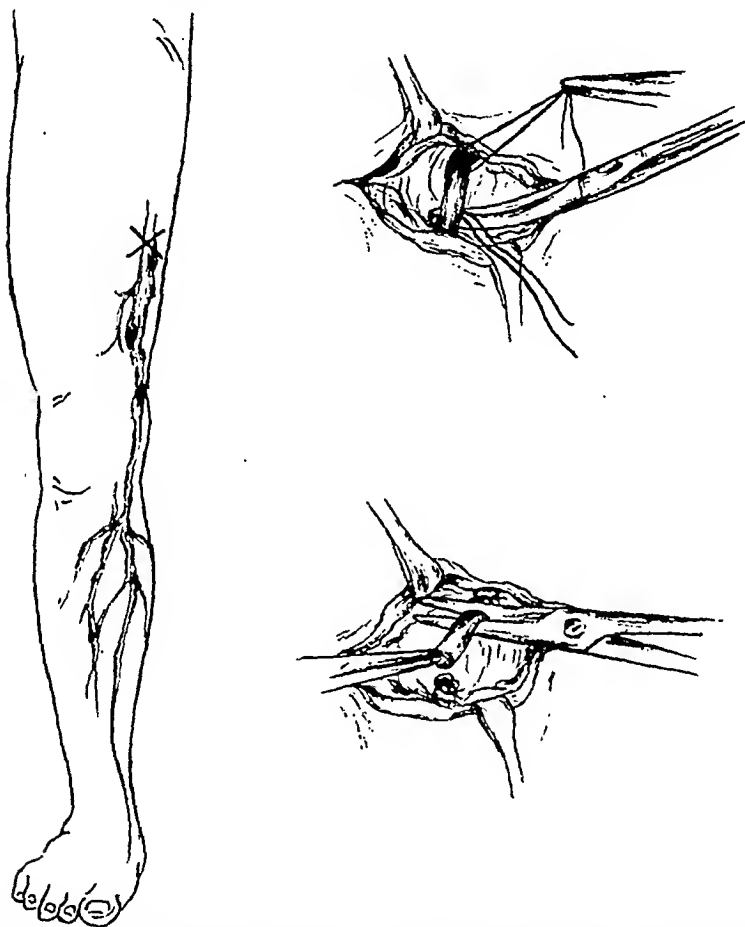


FIG. 15.—The technique of ligation of "blow-outs" below the femorosaphenous junction. With patient standing the site is marked with acriflavine (4 per cent) and iodine. Note that the vein is often under the superficial fascia.

The skin edges are retracted with Allis clamps or small blunt retractors, and the dissection deepened sharply to the superficial fascia which must always be identified and divided. A little blunt dissection usually readily exposes the long saphenous, resting in fatty tissue under the superficial fascia, and proximal to the fascia lata of the thigh. The vein is separated from its bed over several centimeters and plain cat-

gut sutures are placed but not tied around the upper and the lower ends of the freed segment. A nick is made in the lower end of the vein between two mosquito clamps, and a transfusion cannula inserted into

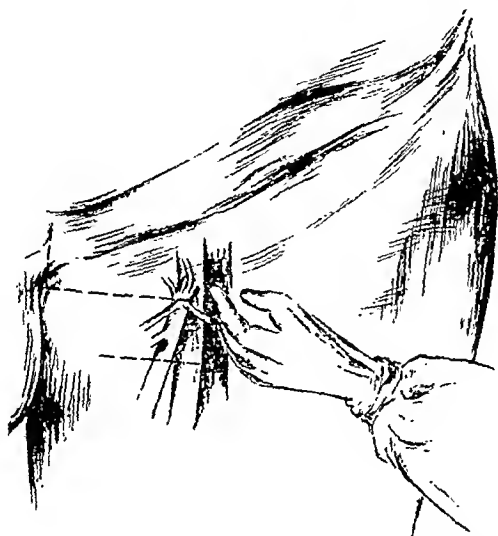


Fig. 16.—Anatomy—The femorosaphenous junction is usually 1.7 cm. below and 3.9 cm. lateral to lateral spine of symphysis. Incision 1 cm. below femorosaphenous point, horizontal and mesialward from femoral vessels. Landmarks: fingers on pulsating artery.

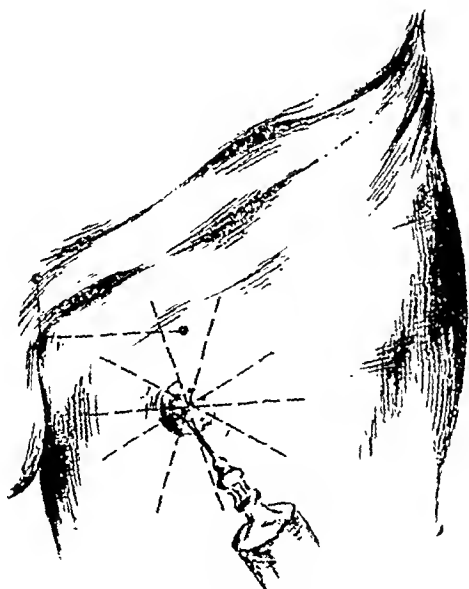


Fig. 17.—Local anesthesia.

the lumen of the vein. The two sutures are then tied, the lower one to prevent leakage around the cannula, and the upper to serve as a retractor on the upper stump, which is to be subsequently resected. The

vein is divided, and the field packed off for injection. The obturator of the cannula is removed, and a Luer-Lok syringe used to inject 2



Fig. 18.—Incision through the superficial fascia. The saphenous vein lies beneath the superficial fascia and on the fascia lata.

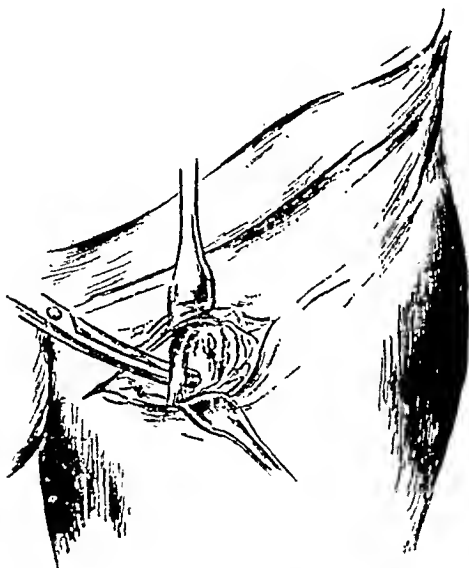


Fig. 19.—Blunt dissection is used to strip up saphenous vein.

to 5 c.c. of 5 per cent sodium morrhuate into the lower end. It is important to use a cannula rather than a needle for this injection, as insertion of a sharp needle into the lumen with the vein collapsed is

difficult. Having completed the injection, the obturator is replaced, the cannula removed, and the lower end of the vein again tied off.

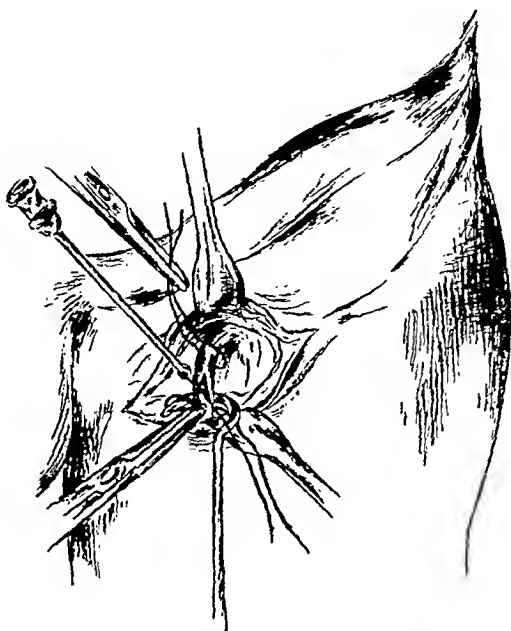


Fig. 20.—A nick cut in vein and a transfusion cannula tied into place. Vein tied off above and divided.

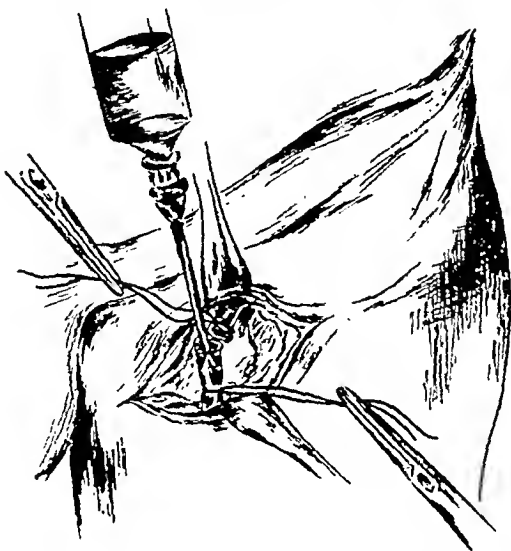


Fig. 21.—Distal portion of vein injected with 3 c.c. of sodium morrhuate, 5 per cent. Cannula removed, distal portion of vein re-ligated and dropped out of site.

Then follows the most difficult part of the operation, the removal of the saphenous stump and division of the branches usually encountered at the femorosaphenous junction. This is somewhat tedious and

vein is divided, and the field packed off for injection. The obturator of the cannula is removed, and a Luer-Lok syringe used to inject 2



Fig. 18.—Incision through the superficial fascia. The saphenous vein lies beneath the superficial fascia and on the fascia lata.

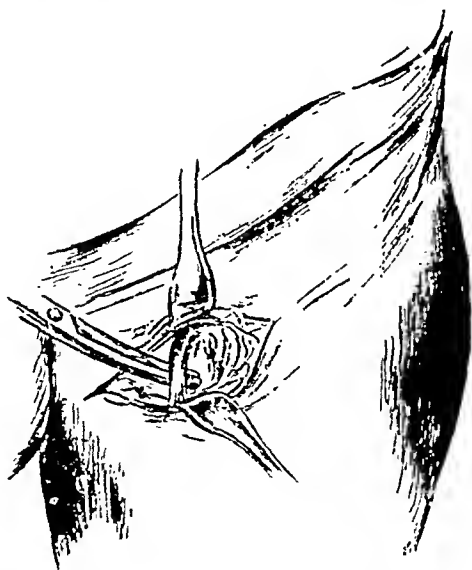


Fig. 19.—Blunt dissection is used to strip up saphenous vein.

to 5 c.c. of 5 per cent sodium morrhuate into the lower end. It is important to use a cannula rather than a needle for this injection, as insertion of a sharp needle into the lumen with the vein collapsed is

of medial superficial femoral veins; (3) a superficial circumflex iliac vein; (4) superficial inferior epigastric veins; and (5) a superficial external pudendal vein. The vein is then doubly ligated flush with the femoral and excised. If properly done, no stump is left that may gradually elongate into a recurring varix; no tributaries are left to dilate and reestablish downward flow; no collaterals are spared to varicose under the strain of increased load. The wound is closed in the usual manner. Interrupted deep sutures are placed to obliterate the dead space; continuous dermal is used for the skin. Occasionally, a small Penrose wick is placed in the wound for twenty-four hours. I arrived at the above described procedure independently, in a constant effort to improve my results in treating varicose veins. A review of

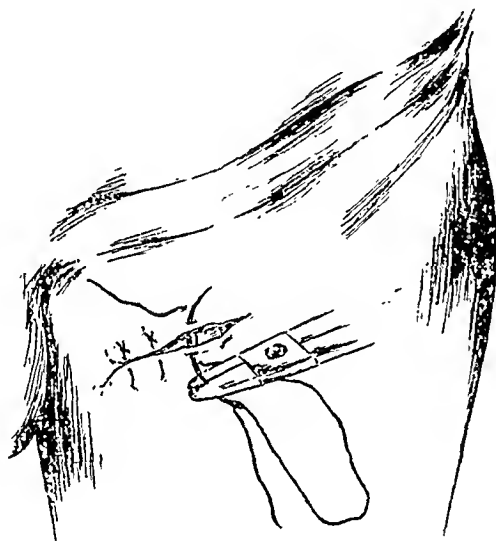


Fig. 24.—Special suture used to give good approximation of wound edges.

the literature early indicated to me how far from original my procedure was, other workers having encountered the same problems and solved them in the same way.

Opinions vary as to the advisability of doing the saphenous injection at the time of the ligation operation as described above. In my judgment, the simultaneous rather than subsequent injection is the procedure of choice. The chief disadvantage is the possibility of rendering the patient bed-ridden because of undue reaction in the injected vein. This is readily avoided by controlling the extent of the vein affected by the injection, by a secondary operation lower in the leg of which I shall say more shortly. The chief advantage of simultaneous injection is that the sclerosing agent is injected in a completely collapsed vein, with greater likelihood of permanent obliteration. Furthermore, the



time consuming, but important. Using the upper ligature for traction, the stump is raised and freed by sharp dissection to its entrance into

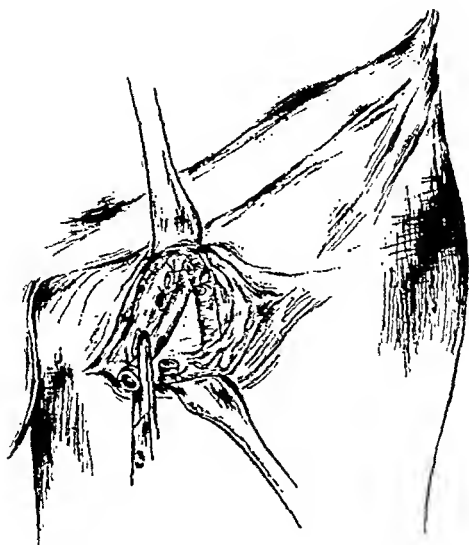


Fig. 22.—Wound retracted upwards, proximal end of vein dissected up to its entrance into femoral. All branches of saphenous and femoral at junction are ligated and divided.

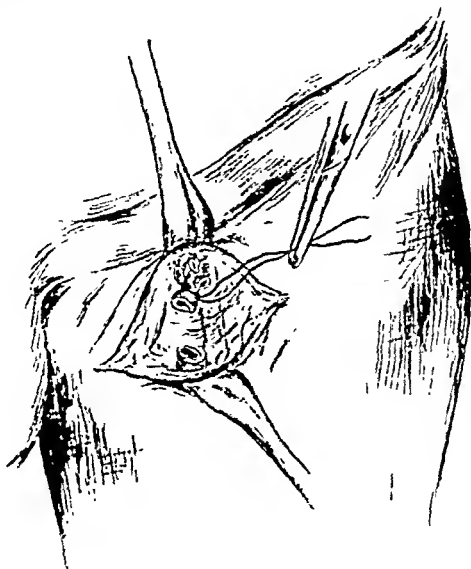


Fig. 23.—The proximal end of vein ligated and divided flush with femoral vein. No stump allowed to remain.

the femoral. The tributaries at the junction are separately dissected and divided between ligatures. These tributaries may be several or all of the following: (1) a lateral superficial femoral vein; (2) a group

## CONCLUSIONS

The injection treatment of varicose veins is adequate for relatively small and isolated varicosities. Recurrence is the almost invariable result, when this method is employed alone, for larger varicosities, directly related to the incompetent long and short saphenous vein. Such cases require interruption of the downward venous pressure at the so-called "blow-out" sites. Ligation of the long saphenous is performed ideally at the femorosaphenous junction, along with division of all tributaries encountered at this site. "Blow-out" sites lower in the leg require separate division below the lowest competent vein valve. In the intelligent use of the tourniquet following the principles of the Trendelenburg test, rests the key to the discovery of the various "blow-out" points. Undue inflammatory reaction following combined ligation and injection can be prevented by a second ligation, lower in the leg, to limit the extent of vein affected by the sclerosing solution. If the principles of combined ligation and injection as outlined in this paper are followed, the treatment of varicose veins should remain simple, ambulatory, and attended by a minimum of recurrence.

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uppermost portion of the varix is occluded by the injection, whereas this end is very difficult to inject at a future date.

The after-care of the combined ligation and injection procedure is simple. The patient is allowed to sit up in bed as soon as he desires and has lavatory privileges in three or four hours. The next morning, he leaves the hospital and resumes his usual activities. During his twenty-four hours in the hospital, large, warm, wet dressings of magnesium sulfate are applied to the injected saphenous to minimize reaction. Strips of elastoplast are placed across the vein in the thigh to support it during the next few days, and the patient wears an Ace bandage about the lower leg. Any veins not obliterated by the saphenous ligation and injection are injected at subsequent office visits. With the downward venous pressure removed, these injections are unusually effective and only a few treatments are required.

#### CONTROLLED INJECTION OF THE SAPHENOUS

Anyone who has used the injection method at all extensively has seen severe lymphedema follow an unexpectedly severe venous reaction. The lymphatics, in intimate association with the veins, are strangulated by the perivenous reaction. The resultant leg swelling may take weeks or months to disappear. I am well aware that some authors advise injection of all the varicosities at one sitting, and recall that Unger, of Leipzig, recommended inserting a ureteral catheter down the saphenous to below the knee and injecting the entire vein as the catheter is withdrawn. Certainly needless leg edema must be produced by such methods. I am sure these ideas are wrong. All the advantages of ligation and simultaneous injections are obtained without undue inflammation, and resultant edema, if the segment of vein injected is limited. To this purpose, I regularly ligate and divide the saphenous just above the knee, immediately before performing the ligation and injection operation in the groin. The gratifying result of a painless postoperative period without unexpected edema is well worth the extra effort.

Reurrences following combined ligation and injection procedures have been rare and usually confined to a few veins in the lower leg. From 1932 to July, 1936, forty-nine cases have been treated by the combined procedures outlined in this paper. The results over the four-year period have been as follows:

The three cases of recurrence had a doubly positive Trendelenburg test, indicating incompetency of the communicating veins.

#### FORTY-NINE CASES OF COMBINED LIGATION AND INJECTION

Cured	44	89%
Fair	2	4%
Recurred	3	7%

## CONCLUSIONS

The injection treatment of varicose veins is adequate for relatively small and isolated varicosities. Recurrence is the almost invariable result, when this method is employed alone, for larger varicosities, directly related to the incompetent long and short saphenous vein. Such cases require interruption of the downward venous pressure at the so-called "blow-out" sites. Ligation of the long saphenous is performed ideally at the femorosaphenous junction, along with division of all tributaries encountered at this site. "Blow-out" sites lower in the leg require separate division below the lowest competent vein valve. In the intelligent use of the tourniquet following the principles of the Trendelenburg test, rests the key to the discovery of the various "blow-out" points. Undue inflammatory reaction following combined ligation and injection can be prevented by a second ligation, lower in the leg, to limit the extent of vein affected by the sclerosing solution. If the principles of combined ligation and injection as outlined in this paper are followed, the treatment of varicose veins should remain simple, ambulatory, and attended by a minimum of recurrence.

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## SPONTANEOUS CLOSURE OF ARTERIOVENOUS FISTULAS

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THE spontaneous closure of small arteriovenous fistulas is not unusual, but little has been written on the subject. Discussions are to be found in Makins' book,<sup>6</sup> and in the studies of Reid,<sup>8</sup> who states that "some of the cases will heal spontaneously during the first six months, especially if the patient and the part are put at rest. Indeed, some arteriovenous aneurysms have been known to heal spontaneously after having been present for from five to eight years (Makins, Cushing<sup>2</sup>)." The most remarkable case is that reported by Dry and Horton,<sup>3</sup> in which the fistula, produced by a bullet passing through the upper third of the right thigh, healed spontaneously after twenty-six years. All those who have done experimental work will agree with Brooks<sup>1</sup> that "even comparatively large fistulae established by careful vessel suture, in most instances close spontaneously."

Reid observed healing in Case 24 of his series. The patient was a white laborer, aged thirty-eight years, with a fistula in the right subclavian region, the result of a bullet wound. There was a very marked thrill and bruit, accompanied by rapid enlargement of the cervical veins. Operation was deferred, and after about two months the thrill and bruit began to disappear and the pulsation became less. At the end of six months the signs of an arteriovenous aneurysm had disappeared. In Reid's Case 25, a fistula occurred in the third portion of the left subclavian artery. The patient, a white laborer, aged forty-one years, had been shot six months previously. At first, the thrill was so marked that "the covers of the bed seemed to quiver." The intensity of the thrill decreased rapidly during the first month; after that it decreased more slowly. At operation, six months after the injury, the fistula was found to be small, and Reid noted that a spontaneous cure might have resulted if he had waited longer.

In Cushing's case (No. 5 in Reid's table), a carotid-cavernous sinus communication, with pulsating exophthalmos, had been present for three years. Cushing ligated the internal carotid artery, but it was only at the end of eight years that the symptoms and signs finally disappeared.

The experience of Makins may be summed up by quotations from his book: "We are well aware . . . . that the general tendency is for these openings to contract in size, and even to close spontaneously. I have observed this latter result in its various stages in two instances

of carotid arterio-venous aneurysm, in which primary consolidation of the sac was induced by proximal ligation of the common carotid artery. In both these cases the venous roar was reduced or disappeared after the operation, only to return to its original strength in a few days. In both it subsequently gradually decreased in strength, and after intervals of fifteen and twenty months respectively, finally disappeared. . . . I have also had the opportunity of observing continuously the slow contraction and eventual complete closure of an arterio-venous communication between the innominate artery and vein, the process extending over a period of five years." He writes on another page: "Clinical evidence is not wanting of early spontaneous closure of arterio-venous communications. Thus, in a man with a traversing bullet wound of the right thigh, ten days after the injury a local arterio-venous murmur was present in Scarpa's triangle, and a loud similar murmur was audible over the base of the heart. A fortnight later, both the local and the cardiac murmurs had completely disappeared, and no sign suggestive of any vascular injury remained."

Plisson's<sup>7</sup> advice on small arteriovenous aneurysms follows: "A primary point appears demonstrated: it is that certain small arterio-venous aneurysms are capable of healing spontaneously (Baudet). Therefore, if the patient does not complain of pain, if the aneurysm does not enlarge, does not threaten any complication, is not accompanied by any annoyance, it is better to abstain from operation. Pozzi observed a carotid-jugular aneurysm to heal thus spontaneously at the end of eight months."\*

Holman,<sup>4</sup> placing emphasis on large communications, sees danger in waiting for the spontaneous closure of some of the fistulas: "If there is early evidence that the heart is increasing in size and that the blood pressure and pulse rate show marked variations on opening and closing a fistula, one may be certain that the lesion will not heal and must be eliminated by operation to avoid further effect upon the heart." Another indication for early operation is exemplified in my own case of arteriovenous aneurysm of the left brachial artery, due to a stab wound, in which, on the eleventh day following the injury, a sudden increase in extravasation of blood with consequent tension and pain in the arm necessitated ligaturing of the artery and accompanying veins. The ligatures were applied 2 cm. below the profunda brachii artery and circulatory disturbances did not result.

#### AUTHOR'S CASES OF SPONTANEOUS (NONOPERATIVE) CLOSURE

CASE 1.—A colored laborer, aged thirty-four years; stab wound, subclavian arteriovenous fistula; venous thrombosis; gradual reduction of venous pressure, increase in arterial pressure, cessation of thrill and diminution of bruit. The patient was stabbed below the middle of the left clavicle with a narrow knife, on Sept. 22,

\*Author's translation.

1935. When admitted, his clothes were saturated with blood and the wound was oozing freely. He was in moderate shock and there was pain on motion of the left shoulder, arm and hand. The arm was cold and there was congestion of the veins, but no neurological changes. The clean-cut wound was closed with silk sutures and pressure was applied, but a large hematoma formed in the posterior axilla, which caused fever and disability.

On the tenth day, a thrill and loud to-and-fro murmur were noted over the swollen, pulsating region beneath the middle and outer thirds of the clavicle. The radial pulse was weaker on the left than on the right; the arterial pressure, left arm, 90/78; right, 145/85. The veins in the left arm were markedly dilated. On the next day, the murmur was not as loud as before, and neither the thrill nor the radial pulse could be felt. Two days later, a feeble pulse was made out on the left. The veins were distended and tortuous, and the patient complained of pain in the region of the shoulder joint. On the following day the pulse could not be felt, and the brachial vein and the veins of the cubital fossa were thrombosed and tender. The murmur continued in the left infraclavicular region. A day later, the arterial pressure in the left arm was 0, on the right, 140/60. The venous pressure on the left was 200 mm. (1 per cent sodium citrate), on the right, 90 mm. An electrocardiogram showed abnormality of the S-T segments, left axis deviation, and sinus tachycardia. The blood Kahn reaction was negative. Red blood count, 3,800,000; hemoglobin (Tallqvist), 75 per cent. For several days there was weakness of the muscles supplied by the median nerve.

On the twentieth day in the hospital, the left radial pulse was very weak and the arterial pressure on this side could not be obtained. On the twenty-third day, the pulse was stronger and the arterial pressure on the left was 112/90, on the right, 145/80. The venous pressure on the left was now 110 mm., on the right, 85 mm. On the twenty-eighth day, the arterial pressure on the left was 134/88, on the right, 155/88. The veins of the left arm were now less distended and the systolic bruit in the left infraclavicular fossa could barely be heard. On the day of discharge, Oct. 21, 1935, the venous pressures were approximately equal on the two sides, at 60 mm. I have not been able to follow this patient further, but there is little question but that the fistula has closed.

CASE 2.—An Irish farmer, aged twenty-eight years; shotgun wound, brachial arteriovenous fistula; visualization by neoskiudan; sudden, complete obliteration of the fistula within twenty-four hours after the injection. The record, made at the time of the second admission to the hospital, April 16, 1934, follows: "The patient is a tall, lean, farm laborer who was injured thirteen weeks ago by a shotgun from a distance of about 80 feet. He was admitted to our wards two days later. Small bullet holes were found scattered from the right wrist to the right shoulder, and there were several over the chest wall. There was moderate infection about most of them, and he was treated for ten days with hot packs. Several of the more superficial bullets were extracted. The patient now says that he felt a thrill over the lower, inner portion of his right arm before he left the hospital, but he did not tell the doctors about it. A roentgenogram taken at the time showed a flattened, irregular bullet at the top of the olecranon fossa, and this was assumed to account for the patient's inability to extend the forearm completely. Evidently no thorough examination of the vessels was made.

"In the interval since the first admission, the patient's wounds have all healed except for slight suppuration around one or two bullets on the medial side of the arm. But, for the past four weeks he has had considerable aching pain in the right forefinger, which spreads at times into his thumb and middle finger. He now milks only with his left hand. The right arm feels heavy and there has been aching above the elbow.

"Examination shows a thrill and a continuous machine-like murmur with systolic accentuation, loudest just medial to the biceps muscle in the lower third of the right arm. It is heard anywhere over the arm, but is not audible when the stethoscope is placed over the right subclavian artery or over the heart. The veins of the arm and forearm are moderately dilated. The fistula is easily obliterated by light direct pressure, and the thrill and bruit disappear when the artery is compressed against the humerus proximally.

"The radial pulse on the right is only slightly weaker than on the left, and the circulation in the forearm and hand at first sight appears good. When the hand is elevated, however, it becomes markedly pale, and when it is depressed it flushes. If the brachial artery is compressed above the level of the fistula without obliterating the communication, the arm and hand become ivory white. The arterial pressure in the affected arm is 120/76, and in the opposite, 110/68. After obliterating the fistula the arterial pressure in the other arm is unaltered (108/68). When the cuff is put on the left forearm, the oscillations due to the arterial pressure are seen easily in the mercury column, but when the cuff is put on the right forearm there are no oscillations. Three pulse readings, at three-minute intervals, were 79, 76, and 76 beats per minute. Pulse rates, taken alternately with these, during times when the fistula was closed off, were 68, 64, and 66, demonstrating a slight, but definite, Branham bradycardiac phenomenon.

"Light compression on the arm above the fistula causes tense filling of the cubital veins, and aspiration of blood from these veins shows admixture with arterial blood."

A determination of cardiac output was made by John Walker Moore and J. Murray Kinsman, who used their dye injection method.<sup>5</sup> The curve was diphasic, indicating by the second rise the effect of the shunting of part of the dye through the fistula. The output in liters per minute (corrected for body surface area) was 5.28. The average normal is 3.79, and the normal for this particular patient, determined later, was 3.65. The increase in output, due presumably to the presence of the fistula, was therefore, 44.7 per cent.

An arteriogram was made by the following method: A tourniquet was applied tightly to the upper arm, and 15 c.c. of neoskiadan were injected into the cubital vein. Roentgenograms, with the needle in place, were taken immediately and were reported upon by S. E. Johnson: "Reexamination of the right elbow . . . shows marked dilatation of the lower third of the basilic vein. The vena comites and brachial artery are well filled from the upper limit of the film downward to its bifurcation. The exact level of the arteriovenous fistula cannot be definitely established."

On the morning after the injection of neoskiadan, the thrill and bruit had disappeared completely. There was no evidence of thrombophlebitis. When seen eight and one-half months later, Jan. 18, 1936, a few of the shot were still palpable, movements were normal at the elbow, there was no evidence of fistula, and the radial pulses were equal in volume.

A second cardiac output determination made thirteen months after obliteration of the fistula showed a monophasic curve and a reduction in output to within the normal range. Here is a comparison of output values before and after obliteration:

	TYPE OF CURVE	CORRECTED OUTPUT (LITERS PER MINUTE)	WORK (KG. METERS PER MINUTE)
Before	Diphasic	5.28	13,875
After	Monophasic	3.65	9,820
Average normal	Monophasic	3.79	4,690



CASE 3.—A colored male, aged thirty-four years; stab wound, brachial arteriovenous fistula; intermittent mechanical compression, followed three months later by cessation of pulsation and thrill; bruit absent on subsequent examination. The patient was admitted to the hospital on April 27, 1935, suffering from shock, the result of two recently inflicted stab wounds, one in the upper left flank and the other on the inner side of the right arm just below the axilla. The wound in the flank was found to be superficial, and both were debrided and closed without drainage. Ecthymosis and diffuse swelling persisted about the upper arm for two weeks, and when this subsided there was noted a more circumscribed, pulsating mass, about three centimeters in diameter, over which a thrill was felt. On applying a stethoscope there was "a constant roar, intensified by a pounding noise, synchronous with each heart beat." The arterial pressure in the unaffected arm was 136/88, but on attempting to read it on the right, no clear-cut sounds could be heard; the roar was continuous from 0 up to 300 mm. and over. The radial pulse volume was very small on the right and by palpation the beats could barely be felt at about 68 mm. The heart-chest ratio in a roentgenogram, exposed at six feet, was 10 to 31 cm. A roentgenkymogram showed greatly diminished excursion of the left ventricle and aorta. An electrocardiogram indicated sinus tachycardia and left axis deviation. The red blood count was 3,730,000; hemoglobin (Tallqvist) 80 per cent. The blood Wassermann reaction was negative. The cardiac output, determined by Moore and Kinsman, was 5.32 liters per minute (corrected for body surface area).

The following note was made eleven months later (March 4, 1936): "When the patient left the ward he was instructed to compress the arteriovenous aneurysm. Each night he lay on his right side and obliterated it completely with the palm of his left hand for half an hour or more at a time. Sometimes he would strap a pad against the mass. He continued to feel the pulsation and thrill for about three months, when both disappeared. None of the signs have recurred. The patient had a complete wrist-drop when he left the hospital, and was unable to use his forearm or any of the muscles in his hand. After about five months, he was able to dorsiflex the wrist, and some of the other motions of the hand have returned.

"Examination now shows a scar one centimeter long on the medial aspect of the right arm, between the biceps and triceps, just below the insertions of the pectoralis major and latissimus dorsi muscles. There is a hard, nontender, fusiform mass in the brachial artery at this level. The artery pulsates strongly above the mass, but below it there is no pulsation. There is no thrill or bruit. The brachial artery cannot be felt in the lower third of the arm. The radial artery is palpable at the wrist, but the impulse is much weaker than on the other side. The arterial pressure in the unaffected arm, where the oscillations begin at 170 and stop at 30, is 140/84. On the right, no arterial sounds can be heard, but oscillations are seen between 160 and 50. Examination of the forearm and hand shows loss of function of the supinator longus, the opponens pollicis, and the first and second lumbrical muscles. There is radial and ulnar weakness as well, with moderate atrophy of the hypothenar eminence, and marked atrophy of the thenar eminence. There are no sensory changes to pin-prick."

#### CONCLUSIONS

1. Small traumatic arteriovenous fistulas often heal spontaneously.
2. Closure appears to be accelerated by spontaneous venous thrombosis or by systematically repeated obliteration by compression.
3. The possibility of the use of sclerosing solutions suggests itself and may perhaps find limited application when damage to the intima can be confined to the fistula and the vessel walls immediately adja-

cent to it. Injection treatment has been used successfully in two small congenital fistulas by Smith and Horton.<sup>9</sup>

4. Fistulas, even when small, increase the cardiac output.

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quality, rhythm regular, no murmurs present. Vessels somewhat sclerotic; B. P. 176/110. The abdomen was greatly distended and tympanitic, and felt like the pneumoperitoneum that is induced in peritoneoscopy. There was only slight tenderness throughout with no rebound tenderness and no muscle guarding. Peristaltic activity was diminished and heard as though at a distance. The area of liver dullness was almost completely obliterated by tympany. No evidence of increased intra-abdominal fluid could be elicited. Genitalia normal male. Rectal examination revealed the presence of hemorrhoids; the prostate was small; high in the culdesac acute tenderness referred to the lower abdomen was obtained on palpation. Extremities thin. Left knee jerk absent. Right Achilles reflex greater than the left. Other reflexes hyperactive. Temperature, 98° F. White blood cell count, 4,200. Urinalysis revealed only the presence of an occasional pus cell.

A tentative diagnosis of the perforation of a hollow intraabdominal viscus with pneumoperitoneum and subcutaneous emphysema was made. In view of his con-

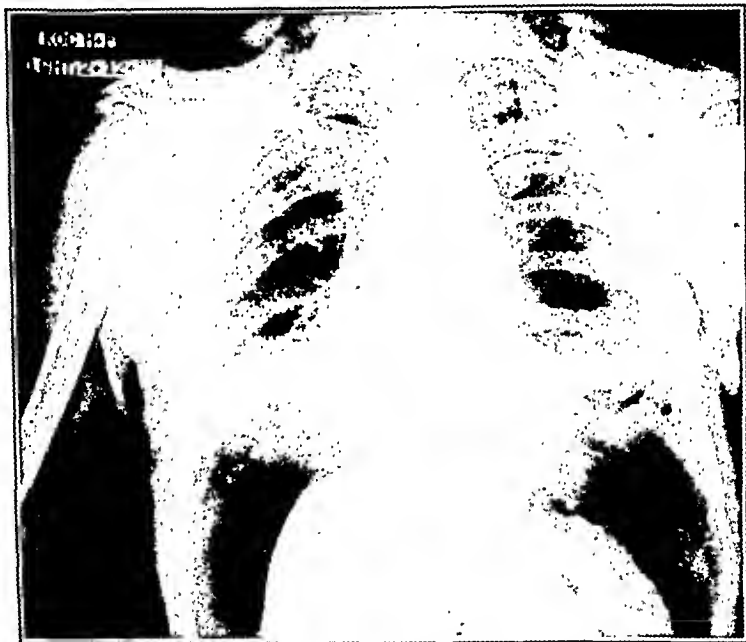


Fig. 1.—Roentgenogram showing the large accumulation of gas beneath the diaphragms and in the tissue of the neck and axillae.

stipation, loss of weight, and cramplike pains, it was thought most likely that he had a perforation of a malignant ulcerative lesion of the colon, or a perforation of the cecum secondary to a malignant occlusion of the colon. Perforation of the duodenum, however, was also kept in mind.

Roentgen ray examination of the abdomen revealed an extensive pneumoperitoneum. In the chest plate the diaphragms were displaced upward and the lung bases were somewhat compressed as a result of the pneumoperitoneum. There was a small amount of gas in the intestines. There was an extensive emphysema of the mediastinum, neck, and chest wall. A barium enema entered the large intestine freely to a point about six inches proximal to the splenic flexure, but no evidence of annular deformity could be demonstrated.

Laparotomy was performed through a right rectus incision under local anesthesia supplemented by ether. As the peritoneum was opened, a large amount of gas

## SUBCUTANEOUS EMPHYSEMA ASSOCIATED WITH PERFORATED PEPTIC ULCER

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**S**UBCUTANEOUS emphysema arising from injury or disease of the chest and respiratory passages is of frequent occurrence on a busy surgical service, but emphysema arising from some solution of the continuity of the gastrointestinal tract is an unusual finding. One of the most interesting sources of subcutaneous emphysema of intestinal origin is that which is seen rarely in association with perforated ulcer of the stomach or duodenum. The physical examination, roentgen ray films, and operative findings in this case serve to illustrate this striking phenomenon.

**CASE REPORT.**—F. K., CGH68429, aged sixty-two years, male, married, white. The patient entered the hospital on Feb. 12, 1937, and gave the history that two days previously while at work he was seized with severe cramplike abdominal pains which seemed to arise in the left upper quadrant of the abdomen but which quickly spread over the entire abdomen without radiation to other parts. On the day before entry the cramps were less severe and he vomited twice some medication that was given to him. On the day of his entry he complained of very little abdominal pain. About one week before entry the patient began to notice an occasional cramplike midabdominal pain and became more constipated than usual. Five days before entry he took a cathartic and had a bowel movement the following day, but he was obstinately constipated thereafter in spite of enemas and medication. There was no history of melena, but he had had some bleeding hemorrhoids many years ago. On the evening preceding his entry into the hospital, his family noticed a slight swelling of the left side of the neck. On the morning of Feb. 12, 1937, while straining at stool attempting to evacuate an enema, a diffuse swelling of the neck occurred rather suddenly. The abdomen had gradually become distended over the previous two days, following the onset of his episode of acute abdominal pain. He had had a cold with a rhinitis, cough, and a small amount of purulent sputum over the previous six weeks. He had a chancre in his youth. Over the past year he had lost ten pounds in weight. There was no history of any sort of digestive disturbance.

Physical examination revealed a thin, pale, sallow white male of about sixty years of age who was in no acute pain or distress. The head was partially bald. Pupils almost completely fixed. Nasal septum intact. Pharynx mildly injected. There were a few dental snags. There was an extensive subcutaneous emphysema of the entire neck and this extended downward over the anterior aspect of the chest, both axillae and to some degree on both upper arms. There was no respiratory embarrassment. Breath and voice sounds were somewhat distant and both diaphragms were high. The trachea was in the midline. The heart sounds were of fairly good

Poensgen<sup>3</sup> gave his inaugural address in 1879 on the subject "Das subkutane Emphysem nach Kontinuitätstrennung des Digestionstrakts, insbesondere des Magens." In his discussion of this treatise Korach<sup>3</sup> states that Poensgen collected illustrative cases, went into the subject exhaustively, and reported a case studied in conjunction with the internist Kussmaul and the pathologist Recklinghausen. The case was one of perforation near the cardia with an extension that spread the muscular fibers of the esophagus. Kussmaul believed that the gas got into the mediastinum through the split fibers of the esophagus, and from the mediastinum finally found its way into the subcutaneous tissues. Recklinghausen held that the gas progressed subperitoneally from the ulcer to the region of the diaphragm from where it went to the anterior mediastinum or to the retroperitoneal cellular tissues and thence found its way to subcutaneous tissue.

Faber, 1885, is quoted by Hurst and Stewart<sup>1</sup> under their discussion of "gastromediastinal fistula." Faber's case was one in which an ulcer of the lesser curvature perforated directly into the mediastinum with resulting mediastinal and subcutaneous emphysema.

Korach<sup>3</sup> states that this symptom is mentioned in large books on the diseases of the stomach, e.g., Boas, Riegel. It is also spoken of in certain collected essays, e.g., Brütt, Mühlham.

Vigyázó,<sup>8,9</sup> in 1926 reported the case of a fifty-two-year-old tabetic in which the diagnosis between peritonitis and a tabetic gastric crisis was difficult. He saw the patient about one-half hour after onset of pain. The discovery of a subcutaneous emphysema about the region of the umbilicus on the abdominal wall aided him in making the diagnosis. At laparotomy he found a pinhead sized perforation of a calloused ulcer of the anterior wall of the duodenum. The emphysema disappeared on the first postoperative day. He has two theories advanced to attempt to explain the condition. First is that the gas might diffuse through the parietal peritoneum. Second is that the gas finds its way subserously either along (a) the hepatoduodenal and round ligaments to the umbilical region, or (b) subserously to the retroperitoneal tissues and then around the flanks to the abdominal wall anteriorly. The first variation of the second theory he believes to be the most likely and the valvelike appearance at the opening of the perforation in his case would tend to substantiate it. He believes the reason for the infrequent occurrence of the condition is the fact that the mechanical conditions at the site of perforation are not favorable for the diffusion of gas in the manner described.

Podlaha<sup>6</sup> in 1926 reported the case of a patient, aged seventy-three years, seen twenty-six hours postperforation who had a greatly distended tympanitic abdomen and subcutaneous emphysema of the left supraclavicular fossa, the jugular notch, and the anterior thoracic wall. At laparotomy he was found to have a perforated ulcer high on the

escaped with a hissing noise and the abdominal distention collapsed. There was a small amount of turbid (dishwater) fluid and an early generalized peritonitis. A small amount of fibrin was present in the right upper quadrant around the duodenum and gallbladder. On the anterior wall of the duodenum there was a small "punched out" (acute) perforated ulcer. No lesion was felt on the posterior duodenal wall. There was no demonstrable emphysema in the ligamentous structures or retroperitoneal region as far as exploration was possible. The ulcer was cauterized and closed with a miniature Heineke-Mikuliez pyloroplasty. The abdomen was closed with silver wire without drainage.

The postoperative course was stormy. The subcutaneous emphysema gradually subsided. He developed the signs of a progressive generalized peritonitis with

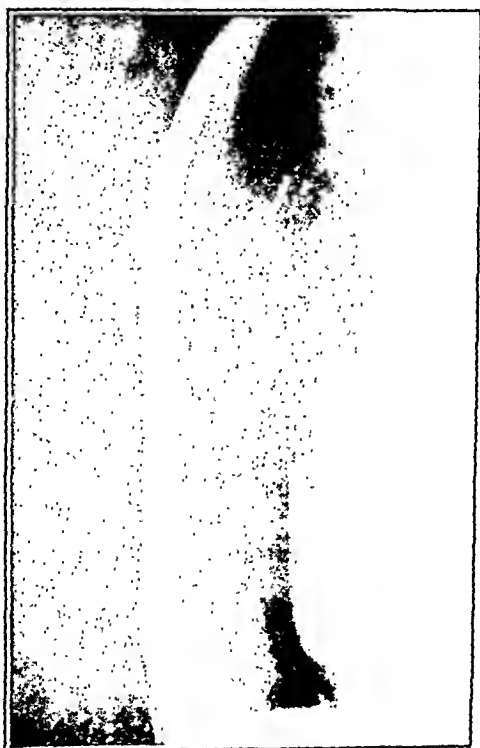


Fig. 2.—Lateral roentgenogram of the abdomen showing the extensive pneumoperitoneum.

fever, acute abdominal tenderness, and distention. The wound became infected and he developed a terminal bronchopneumonia and expired on the eighth postoperative day. Autopsy was refused.

Demarquay<sup>3, 5</sup> is said to have been the first to describe subcutaneous emphysema after the perforation of the gastrointestinal tract when the parietal peritoneum is injured.

Roger's<sup>2</sup> work, "*De l'emphyseme generalise*," was prepared on the basis of a case of very widespread subcutaneous emphysema following the perforation of a tuberculous ulcer.

this was not a phlegmonous emphysema. He calls attention to the particular interest of the emphysema spreading after death and to the identification of the gas as hydrogen. He gives a presumptive formula for the formation of hydrogen gas from the dextrose of the partially digested food in the stomach. He hypothesizes also that the large amount of gas generated in the partially occluded stomach might have been responsible for the perforation. From the study of his case, Korach believed that the gas diffused directly through the peritoneum where its structure was altered or destroyed by the inflammatory process.

Kellogg<sup>2</sup> in his monograph *The Duodenum*, 1933, deals very briefly with emphysema: "Emphysema of the surface of the body, which is infrequent, suggests perforation of the digestive tract or an injury involving the respiratory tract."

Examination of those recent texts and systems of surgery at our disposal reveals no mention of this unusual phenomenon.

From this brief survey of the literature it seems that the explanation of the appearance of subcutaneous emphysema in perforated ulcer of the stomach or duodenum is not clear. Certainly in our case the route followed by the gas from the stomach to mediastinum and the subcutaneous tissues is not obvious.

Two theories as to the possible routes of diffusion have been advanced:

1. Diffusion directly through the parietal peritoneum. This would seem to be particularly feasible in cases where the pneumoperitoneum was extensive and under pressure (as in our case) and where the parietal peritoneum was greatly damaged by the inflammatory process (as in Korach's case).

2. The diffusion of the gas from the site of perforation subserously (a) along the peritoneal covered ligamentous structures about the stomach and duodenum and then to the neck by way of the mediastinum or via the round ligament (of the liver) to the umbilical region; (b) to the retroperitoneal areolar tissues and then around the abdominal wall or up the mediastinum to the neck. The cases of Podlaha and Vagyázó tend to support the first section of this theory as do the experiments of Podlaha on the injection of hydrogen peroxide subserously about the stomach and duodenum in cadavers and in dogs. This theory requires, however, that certain mechanical conditions be present at the site of perforation; viz., a valvelike flap or an irregular linear perforation that would permit the "pumping" of the gas into the subserous tissues from the stomach.

Vagyázó<sup>3</sup> and Korach<sup>3</sup> brought up the possibility of a ruptured pulmonary emphysematous bleb into the mediastinum as the origin of emphysema in Podlaha's case. The same criticism might be applied to our case. Although there was no roentgen ray or physical evidence of



lesser curvature near the cardia of the stomach. His emphysema subsided over a period of five days. He expired on the fourteenth day with a left subphrenic abscess. Podlaha states that the perforation is usually located so that the gaseous contents of the stomach escape into the peritoneal cavity. If, however, the perforation occurs high on the lesser curvature, or on the posterior duodenal wall near the insertion of the hepatoduodenal ligament, and if the perforation is small with a flap valve or irregular wall, the gas can get into the interstitial tissues and find its way to the subcutaneous regions. In the case of the duodenal ulcer it may go to the region of the umbilicus and in those ulcers near the cardia it goes to the left supraclavicular fossa. Experimentally in ten cadavers and in three dogs, Podlaha demonstrated the methods of diffusion of gases from the various parts of the stomach and duodenal regions by injecting hydrogen peroxide into the subserous tissues. He found that from injections made in the region of the pylorus the material passed along the hepatoduodenal and round ligaments (of the liver) to the region of the umbilicus. From injections made near the cardia, the material made its way principally by way of the phrenicoesophageal ligament and aortic hiatus into the posterior mediastinum, through the cleavage planes to the neck, and to the subcutaneous tissues. Podlaha gives three possible reasons for the rarity of subcutaneous emphysema with perforated ulcer:

1. Perforations on the cardia and posterior wall of the duodenum are rare.
2. The perforation must be small and in the form of a zig-zag fissure or valvelike.
3. The interstitial connective tissue must not contain too much fat.

Korach<sup>3, 4</sup> in 1927 reported the case of a thirty-six-year-old man who was seen about eight hours postperforation with a large pneumoperitoneum and a small area of emphysema about the region of the umbilicus. The patient appeared to be dying at that time. Korach saw the cadaver a short time later and the emphysema had spread over the face, neck, left orbit, chest wall, and over the anterior abdominal wall to the flanks. At postmortem examination a large amount of gas escaped from the peritoneal cavity with a hissing sound. This gas exploded, when ignited, with a blue flame. The gas from the subcutaneous areas behaved in a similar manner. On the visceral and parietal peritoneum in several places were dark necrotic patches. There was an emphysema in the peritoneal leaves of the mesentery, colon, ileum, and root of the mesentery. The stomach was dilated and the pylorus almost occluded. High on the lesser curvature near the cardia was a large discolored area containing at its center a circular, smooth-walled perforation. There were about three liters of dark fluid in the abdomen containing food particles, principally partially digested bread and potato. He emphasizes that

this was not a phlegmonous emphysema. He calls attention to the particular interest of the emphysema spreading after death and to the identification of the gas as hydrogen. He gives a presumptive formula for the formation of hydrogen gas from the dextrose of the partially digested food in the stomach. He hypothesizes also that the large amount of gas generated in the partially occluded stomach might have been responsible for the perforation. From the study of his case, Korach believed that the gas diffused directly through the peritoneum where its structure was altered or destroyed by the inflammatory process.

Kellogg<sup>2</sup> in his monograph *The Duodenum*, 1933, deals very briefly with emphysema: "Emphysema of the surface of the body, which is infrequent, suggests perforation of the digestive tract or an injury involving the respiratory tract."

Examination of those recent texts and systems of surgery at our disposal reveals no mention of this unusual phenomenon.

From this brief survey of the literature it seems that the explanation of the appearance of subcutaneous emphysema in perforated ulcer of the stomach or duodenum is not clear. Certainly in our case the route followed by the gas from the stomach to mediastinum and the subcutaneous tissues is not obvious.

Two theories as to the possible routes of diffusion have been advanced:

1. Diffusion directly through the parietal peritoneum. This would seem to be particularly feasible in cases where the pneumoperitoneum was extensive and under pressure (as in our case) and where the parietal peritoneum was greatly damaged by the inflammatory process (as in Korach's case).

2. The diffusion of the gas from the site of perforation subserously (a) along the peritoneal covered ligamentous structures about the stomach and duodenum and then to the neck by way of the mediastinum or via the round ligament (of the liver) to the umbilical region; (b) to the retroperitoneal areolar tissues and then around the abdominal wall or up the mediastinum to the neck. The cases of Podlaha and Vagyázó tend to support the first section of this theory as do the experiments of Podlaha on the injection of hydrogen peroxide subserously about the stomach and duodenum in cadavers and in dogs. This theory requires, however, that certain mechanical conditions be present at the site of perforation; viz., a valvelike flap or an irregular linear perforation that would permit the "pumping" of the gas into the subserous tissues from the stomach.

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## THE USE OF ZINC PEROXIDE IN MICROAEROPHILIC INFECTIONS

J. E. RHOADS, M.D., PHILADELPHIA, PA.

*(From the Surgical Clinic of the Hospital of the University of Pennsylvania and the Harrison Department of Surgical Research, University of Pennsylvania)*

ZINC PEROXIDE was introduced for surgical use by Meleney<sup>1</sup> in 1935. Its peculiar value lies in its ability to liberate oxygen over a period of many hours which renders it nearly specific in certain anaerobic infections. The fact that it is practically devoid of irritant properties is an additional advantage of great importance.

In 1935 Meleney<sup>1</sup> reported a group of cases of spreading ulceration of the abdominal wall associated with a hemolytic microaerophilic streptococcus. No anaerobic cultures were made from the first case in the group which was included on the basis of clinical similarity to the remaining five. In all of these hemolytic streptococci were found on anaerobic culture. In two cases the organism also grew under aerobic conditions.

These infections usually start from a wound, either operative or traumatic, and run a very chronic course. Moderate fever is frequent. Pain may be severe but is inconstant. The lesion presents a dirty sloughing base. It slowly undermines the surrounding skin, breaking through to form sinuses opening a short distance from the margin of the original ulcer. These openings gradually enlarge to form secondary ulcers, which finally spread and coalesce with the primary one.

The lesions have been extremely refractory to the usual methods of treatment. A wide variety of antiseptics have been used without success. Repeated excision has, as a rule, been unavailing. Roentgen therapy has been tried without success. In the latter three cases of Meleney's series, zinc peroxide was applied with prompt improvement and subsequent complete healing. Later Meleney<sup>2, 3, 4</sup> reported the use of zinc peroxide in a variety of lesions due to anaerobic and microaerophilic organisms.

Zinc peroxide is a fine powder which is not available in pure form. Commercial brands contain 40 to 50 per cent of the peroxide, the remainder being composed of the hydroxide and the oxide. There is a great difference in the effectiveness of the products of various manufacturers which appears to be due not to the purity of the chemical but to an obscure difference in the availability of the oxygen.

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Received for publication, June 17, 1937.

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This association of emphysema with perforated ulcer does not lend itself to the same easy explanation that can be advanced for the emphysema that is sometimes reported following operative procedures on the intestinal tract or penetrating injuries of the abdomen because in these situations the parietal peritoneum is broken.

It must be said that the phenomenon of subcutaneous emphysema seen with perforated ulcer should not be confused with the phlegmonous gaseous infiltrations that sometimes occur following the retroperitoneal laceration of the duodenum, colon or rectum.

Korach's studies on the hydrogen content of the gas from the peritoneal cavity and emphysematous tissues in his case are interesting but inconclusive because they were done postmortem.

#### SUMMARY

1. A case of perforated duodenal ulcer associated with an extensive pneumoperitoneum and a subcutaneous emphysema of the entire neck, chest wall, axillae, and upper arms is reported.

2. The available literature regarding similar cases is reviewed briefly.

#### CONCLUSION

A completely satisfactory explanation of the occurrence of subcutaneous emphysema in rare cases of perforated stomach or duodenal ulcer is not available at the present writing.

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During the past two years, two patients with chronic leg ulcers infected with microaerophilic hemolytic streptococci have been admitted to the Hospital of the University of Pennsylvania. Since they demonstrate the great value of zinc peroxide, the salient points of their histories have been included.

CASE 1.—The patient (R. K.) was a twenty-two-year-old man who developed an indurated infected area over the left tibia in March, 1936. This was incised early in April. After it had drained for three weeks without tending to heal, the patient



Fig. 2.—R. K. End-result of ulcer shown in Fig. 1 after treatment with zinc peroxide.

came to the Surgical Out-Patient Department of the Hospital of the University of Pennsylvania, on April 27, 1936. At that time there were two shallow punched-out ulcers about  $\frac{3}{4}$  of an inch in diameter, situated close together over the left tibia. These were treated with gelatine boots for one month with complete healing of one ulcer but not of the other. This remained open and in the course of a few weeks extended and the skin in an adjacent area broke down.

The area was drained on May 28, 1936, and for two weeks thereafter clean granulation tissue formed at the base. There was, however, a marked cellulitis about the ulcer which persisted. Three x-ray treatments were given with transient improvement. On June 19 another ulcer formed 0.5 cm. below the old one. On June 26 it was noted that the adjacent skin was being undermined, and this area was excised. During the next few weeks the ulcers coalesced to form an area 6.5 cm. by 3.5 cm. with a few small sinuses opening nearby.



A simple test suggested by Meleney<sup>4</sup> for determining whether a given lot is effective consists in shaking a few grams of the powder in a test tube filled with water and allowing it to stand. The effective zinc peroxide forms a suspension which precipitates rapidly, leaving the supernatant liquid clear, and forms visible bubbles of oxygen in the precipitate within two or three hours.

On the basis of the information at hand, the product of the DuPont Chemical Company, of Niagara Falls, New York, prepared for medicinal

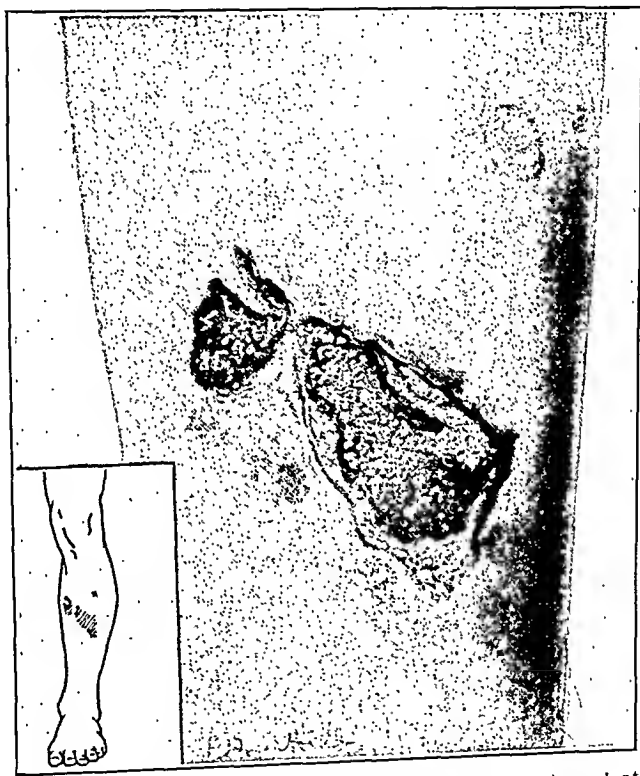


Fig. 1.—R. K. Leg ulcer due to microaerophilic hemolytic streptococci at the time of admission to the hospital.

purposes is the most reliable. The manufacturers advise heating the powder to 140° C. for four hours shortly before it is used.

It is applied in the form of a thin paste directly to the ulcer and should be covered with wax paper or gauze impregnated with zinc oxide ointment to prevent drying. Usually it forms a thin cake moulded by the walls of the ulcer. This should be removed once a day and replaced with a freshly prepared paste.

It has been the practice on Dr. I. S. Ravdin's service at the Hospital of the University of Pennsylvania to debride the ulcer just before be-

ginning the treatment and to facilitate epithelization with pinch grafts soon after the ulcer has become clean and started to granulate.

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On July 27, 1936, the patient was admitted to the surgical wards. At that time the ulcer had the appearance shown in Fig. 1 and measured 8 cm. in length and 3.5 cm. in width. X-ray of the tibia and fibula was negative.

Pus from the ulcer was cultured and showed hemolytic streptococci in pure culture both aerobically and anaerobically. On Aug. 3 zinc peroxide paste was applied. A fresh paste was prepared each day and the ulcer covered with it. Improvement was noted within three days.

By Aug. 13 nearly the whole area was epithelized. The remainder was clean and pinch grafts were applied. A number of these grew and epithelization was complete on Aug. 20. The patient was last seen in April, 1937. The ulcer has remained healed and painless (Fig. 2).

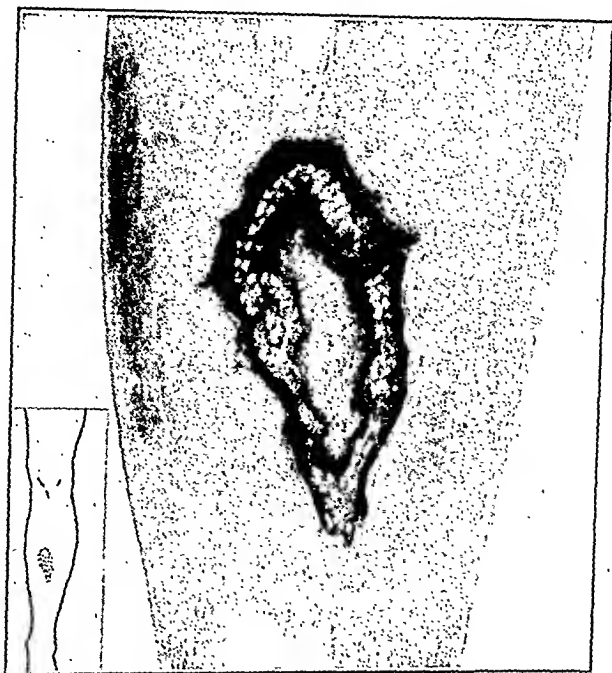


Fig. 3.—L. H. Leg ulcer due to microaerophilic hemolytic streptococci. This ulcer started over three months earlier from a minor abrasion.

CASE 2.—L. H., a white woman, thirty-seven years of age, was admitted to the Hospital of the University of Pennsylvania on March 4, 1937, with an ulcer 5.5 cm. long and 3.5 cm. wide on the right leg. It was situated over the subcutaneous portion of the tibia about 5 inches below the knee.

The lesion started from a slight abrasion caused by bumping a chair Dec. 16, 1936. At first there was considerable swelling and redness. Drainage started at the end of a week. After Jan. 1 the patient stayed in bed and the swelling subsided. Treatment consisted in salves, hot wet dressings, and Scharlach R.

At the time of admission to the hospital the ulcer was 0.5 cm. deep and irregularly oval in shape (Fig. 3). The edges were ragged and the bottom was covered with unhealthy granulation tissue covered with pus.

X-ray examination showed no underlying bone pathology.

A culture was taken and the unhealthy granulations and a portion of the edge of the ulcer excised and studied histologically. The culture showed hemolytic streptococci both aerobically and anaerobically. The pathologist reported the excised tissue as a nonspecific ulcerative granuloma.

The ulcers were covered with a thin paste of zinc peroxide which was renewed daily. Clean granulations grew up from the bottom. On March 11, 1937, seven Staige-Davis grafts were taken from the thigh and placed on these granulations. All the grafts took and the wound was about half covered with epithelium at the time the patient left the hospital on March 18.

Five days later the whole area was covered except for a spot 8 mm. in diameter. Healing was complete on April 2, 1937, and the patient has remained well (Fig. 4).

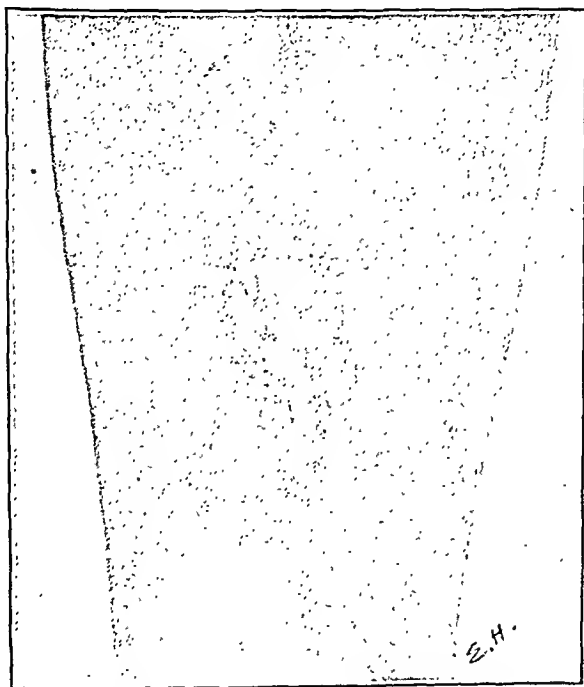


Fig. 4.—L. H. Ulcer shown in Fig. 3 after treatment with zinc peroxide.

In neither of these cases was the organism an obligate anaerobe. The ulcers were not on the abdomen and the patients were nearly afebrile. Otherwise, they correspond very closely to the original cases described by Meleney. While a majority of the cultures obtained by Meleney grew only under anaerobic conditions, two of them also grew in the presence of air as these did. In later reports Meleney<sup>2, 3, 4</sup> has described ulcers in locations other than the abdomen which have apparently had the same etiology as those in his earlier paper and have responded to the same treatment.

Recently a patient presented himself for treatment of a chronic high perirectal abscess which began just below the promontory of the sacrum

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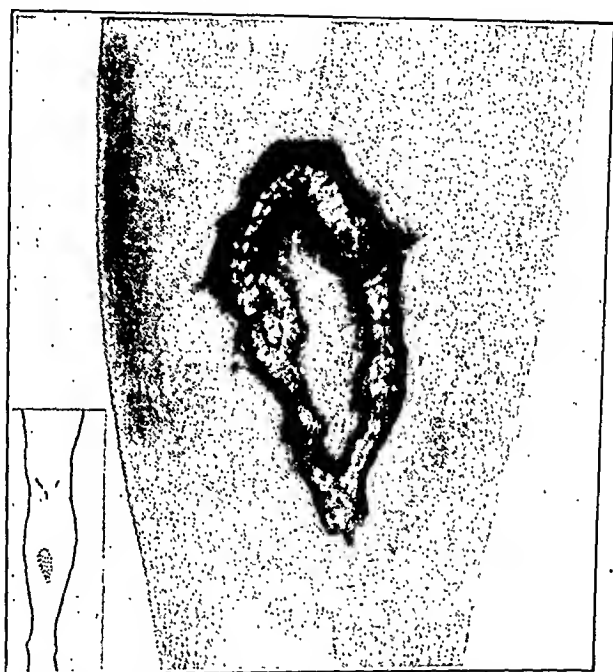


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# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## RECENT ADVANCES IN THE TREATMENT OF VARICOSE VEINS\*

GEORGE SUMMERS JOHNSON, M.D., NASHVILLE, TENN.

(From the Department of Surgery, Vanderbilt University)

### INTRODUCTION

THE following discussion is confined to varices of the lower extremities. Only that treatment which deals with the varicosities themselves will be discussed. No attempt will be made to discuss the treatment of varicose ulcers other than the removal of the cause. Thrombophlebitis or other allied diseases of the venous system of the lower extremity will not be considered.

No attempt is made in this paper to cover the entire development of the treatment of varicosities. The general historical development is outlined and the more important phases of modern therapy are emphasized.

There has never been any wholly satisfactory treatment for varicose veins of the legs. This fact is emphasized by the numerous different treatments or modifications of treatments advocated and by the enthusiasm with which new treatments or new modifications have been seized upon. In all types of therapy tried there has been a relatively large percentage of recurrences in cases followed any length of time, in spite of the fact that the immediate results of most types of treatment have usually been encouraging. It seems the most logical reason for this state of affairs is that many types of therapy have been devised without taking into consideration the underlying pathology of various veins.

No types of therapy carried out for the relief of varicose veins of the lower extremities are new at the present time. All have been tried out before, have been discarded, and have reappeared. Their reappearance, however, has been marked by a distinct increase in the knowledge of the fundamental factors concerned and with more knowledge of the proper selection of cases, as well as purely technical improvements.

### HISTORY OF THE TREATMENT OF VARICOSE VEINS

The recognition and the treatment of varicose veins of the lower extremities is as old as medical literature. Hippocrates<sup>1</sup> described a method of obliteration of a varix by passing needles into the veins. It

Received for publication, Nov. 5, 1937.

and from which a nonhemolytic streptococcus was cultured by anaerobic methods. The abscess opened into the rectum about 4 inches above the anus.

In this case zinc peroxide was diluted to the consistency of whitewash and administered daily as a low retention enema in amounts of 3 to 6 ounces.

#### CONCLUSIONS

Two typical cases of chronic undermining ulcer due to microaerophilic hemolytic streptococci are presented. Both healed rapidly after the use of zinc peroxide.

Zinc peroxide may be introduced into the large bowel with impunity and has proved useful in a case of perirectal abscess associated with a nonhemolytic streptococcus which grew anaerobically.

In the infrequent but refractory ulcers described above, zinc peroxide is nearly specific. As no other form of treatment has proved satisfactory in these cases, it is a needed addition to the surgeon's pharmacopoeia.

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# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## RECENT ADVANCES IN THE TREATMENT OF VARICOSE VEINS\*

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### INTRODUCTION

THE following discussion is confined to varices of the lower extremities. Only that treatment which deals with the varicosities themselves will be discussed. No attempt will be made to discuss the treatment of varicose ulcers other than the removal of the cause. Thrombophlebitis or other allied diseases of the venous system of the lower extremity will not be considered.

No attempt is made in this paper to cover the entire development of the treatment of varicosities. The general historical development is outlined and the more important phases of modern therapy are emphasized.

There has never been any wholly satisfactory treatment for varicose veins of the legs. This fact is emphasized by the numerous different treatments or modifications of treatments advocated and by the enthusiasm with which new treatments or new modifications have been seized upon. In all types of therapy tried there has been a relatively large percentage of recurrences in cases followed any length of time, in spite of the fact that the immediate results of most types of treatment have usually been encouraging. It seems the most logical reason for this state of affairs is that many types of therapy have been devised without taking into consideration the underlying pathology of various veins.

No types of therapy carried out for the relief of varicose veins of the lower extremities are new at the present time. All have been tried out before, have been discarded, and have reappeared. Their reappearance, however, has been marked by a distinct increase in the knowledge of the fundamental factors concerned and with more knowledge of the proper selection of cases, as well as purely technical improvements.

### HISTORY OF THE TREATMENT OF VARICOSE VEINS

The recognition and the treatment of varicose veins of the lower extremities is as old as medical literature. Hippocrates<sup>1</sup> described a method of obliteration of a varix by passing needles into the veins. It

Received for publication, Nov. 5, 1937.



is interesting to note that this first recorded attempt to treat varicose veins was an attempt to obliterate them in situ and is of course exactly the same in theory as the modern so-called injection treatment of varicose veins.

Mayo,<sup>72</sup> in speaking of the history of the treatment of varicose veins, mentions puncture with the Paquelin canterly or with the electrocanterly, cutaneous and subcutaneous suture and ligature as practiced by Valpeau and Delpech. These were also methods of obliterating veins in situ which depended upon thrombosis followed by fibrosis.

The first surgical interference that is referred to in the literature is the ligation of a varicose vein above an ulcer, performed by Celsus<sup>14</sup> in the first century. This has also been referred to by Edwards,<sup>33</sup> who further states that the same procedure was carried out for the same purpose by Paré in 1579 and by Howe in 1797. De Takats<sup>30</sup> states that Howe advocated ligation of veins above ulcers and that his results were excellent except for the sepsis following operation. Brodie<sup>10</sup> in 1846 emphasized the rationale of ligation, especially the saphenous, but also recommended other methods of blocking the vein, such as by compresses or tampons (also referred to by Waimack<sup>103</sup>). In 1891 Trendelenburg<sup>100</sup> advocated ligating the saphenous vein above the knee for the relief of symptoms due to varicose veins.

Since that time the operation has been recommended by numerous other surgeons, most recently by De Takats,<sup>27, 29, 30</sup> in conjunction with injection. Edwards<sup>33</sup> gives an extremely interesting chart showing the approximate site of ligation practiced by different men. It is interesting to note that with few exceptions the more modern the surgeon, the higher the site of ligation. As has been stated, ligation alone of the saphenous vein or of one of its tributaries has never proved a wholly satisfactory procedure. Lower ligation merely shut off the back-flow of blood above one certain point, usually an ulcer, and therefore improved the circulation at that point. The extremity as a whole, however, still retained varicosities. Although the improvement was often sufficient to heal the ulcer, collateral circulation would usually form around the obstruction and the condition would revert to its original status. With the development of surgery in general and especially with the decrease in danger from infection, more complicated operations were devised.

Schede<sup>88</sup> in 1877 described his operation, which consisted of a more or less extensive division between ligatures of the superficial veins above an ulcer. In 1884 Madelung<sup>63</sup> published the method with which his name is associated. This consisted in the complete extirpation of the entire greater saphenous vein and of as many of its branches as seemed indicated.

Thus, for a time, there were three well-recognized operations for varicose veins: those of Trendelenburg, Schede, and Madelung. Gen-

erally speaking, the two former operations seem to have given rather disappointing results, and the later operation was of greater magnitude than many cared to undertake. Miller<sup>74</sup> in 1906 reviewed the results of these three operations as carried out at the Johns Hopkins Hospital. He stated that the Trendelenburg operation had been carried out on nineteen patients, and the Madelung on only five. He further stated that these five cases were all from among the early admissions to the hospital and could not, therefore, be traced. He thought this unfortunate, since he considered that probably this type of operation was followed less frequently by recurrence than either the Trendelenburg or the Schede operation.

In 1899 Casati, referred to by Miller,<sup>74</sup> described a method of tearing out the vein through multiple short incisions. In 1905 Keller<sup>50</sup> advocated stripping the saphenous vein. For this he used a small wire, which stripped out the vein subcutaneously by completely everting it. A year later C. H. Mayo<sup>72</sup> introduced the vein-stripping operation that has been most widely used. Another modification of this operation is that devised by Babcock,<sup>2</sup> the principle in all cases being the complete extirpation of the great saphenous vein without extensive incision and dissection. Stripping the veins below the knee is impracticable or impossible because of the complicated and frequent branching of the veins.

The most satisfactory operative procedure finally evolved combined the stripping of the entire saphenous vein above the knee and the extirpation en masse by dissection of all the veins below the knee. This operation has been particularly advocated by Brooks,<sup>11</sup> Homans,<sup>44-47</sup> and many others. The complete operation is seldom used now, but it was the procedure of choice until a comparatively few years ago. It is interesting to note that Keller,<sup>50, 51</sup> who has been mentioned as one of the first to perfect an operation for vein stripping, described in 1924 an ingenious method of obliterating veins by suture. He used this on the varicosities of the lower leg in connection with the stripping of the saphenous vein. This procedure was essentially obliteration by thrombosis without extirpation. It had many advantages over the complete operation as described above, the chief objections to complete extirpation of the veins below the knee being prolonged hospitalization, the usual requirement of a general anesthetic, the danger of infection and embolism, and the danger of sloughing of skin flaps with delayed healing. The results of the complete operation (stripping of the saphenous vein and extirpation of the varicosities) were excellent. The magnitude of the procedure, however, was out of proportion to the seriousness of the condition.

#### HISTORY OF THE INJECTION TREATMENT OF VARICOSE VEINS

The treatment of varicosities by injecting into them some thrombus-producing agent is of course the same in principle as the ones previously described as methods used to obliterate the veins in situ. The actual in-

jection of varicose veins, however, depended upon and soon followed the invention of the Pravaz syringe in 1851. According to De Takats and Quint,<sup>26</sup> Pravaz injected perchloride of iron into varicose veins as early as 1853. In 1855 Desgranges<sup>23</sup> injected six cases of varicose veins with iodotannic solution. These injections were without accident, but apparently they were accompanied by a great deal of pain. In these early days of injection treatment there were probably a relatively small number of cases treated and these mostly in European clinics. Many different solutions were used, however, among them being alcohol in various solutions, Lugol's solution and phenol (De Takats, Quint, Tillotson,<sup>24</sup> and Crittenden<sup>24</sup> and Blackford<sup>8</sup>). These attempts fell into disrepute because of the severe reaction due to the toxicity and extremely irritating properties of these drugs. Sepsis may have played some part in these early attempts, but most of the solutions used at that time were strongly antiseptic.

In the latter 1870's there was developed in Continental clinics, particularly in Vienna, what Colt<sup>17</sup> refers to as "the era of perivenous injection." This applied not only to varicose veins, but to hemorrhoids, rectal prolapse, varicocele, etc. In these were used such solutions as ergot, alcohol, iron perchloride, chloral, phenol, etc. This type of treatment caused obliteration of veins in situ by fibrosis and was in reality much more similar to the older methods of obliteration previously mentioned than to the treatment we now speak of as injection treatment of veins. This type of treatment has of course been entirely given up in the case of varicose veins, but it is exactly the same as used today in the injection treatment of hemorrhoids and varicocele, except for the solutions used. It is rather important to emphasize that the obliteration of varicose veins by the intravenous injection of a thrombus-producing substance as practiced at the present time is entirely different in principle to the injection treatment of hemorrhoids, varicocele, hydrocele, and hernia. The latter is based upon exactly the same principle as treatment of varices by perivenous injection; viz., the setting up of a severe inflammatory process and the production of a large amount of scar tissue which by its contraction obliterates veins, venous sinuses, or serous cavities. The treatment of varicose veins by perivenous injection was found to be wholly unsatisfactory (Colt<sup>17</sup>).

The recent development of the treatment of varicose veins by injection was given impetus by Sicard,<sup>60, 61</sup> Model,<sup>55</sup> and Linser<sup>60, 61</sup> and their coworkers. Sicard and his coworkers and Linser discovered the sclerosing properties of drugs used in the treatment of syphilis. Sicard<sup>61</sup> in 1922 reported curing varices by the injection of sodium salicylate, later using other solutions. Linser<sup>60</sup> noted the excellent venous thrombosis and obliteration sometimes produced by the intravenous injection of bichloride of mercury in the treatment of syphilis. In 1925 he reported the successful treatment of varicose veins by this method and in

1925<sup>61</sup> reported the same thing, using 15 to 25 per cent sodium chloride. De Takats and Quint<sup>26</sup> give credit to these men for the development of the use of hypertonic solutions in the treatment of varicose veins. The therapeutic connection between varicose veins and syphilis was carried a step further by Borcherts,<sup>9</sup> who in 1927 reported curing a patient simultaneously of varicose veins and syphilis by intravenous injection of salvarsan. From this time on until recently, most of the advances in the injection treatment of varicose veins had to do almost entirely with the solutions used.

#### SOLUTIONS

Up to the time of Sicard and Linser the various solutions of mercuric salts had perhaps been the most widely used of all solutions, the chief objection to them being their toxicity which necessarily limited the dose given. There were other disadvantages, but these were largely shared by all solutions used until more recently. In 1919 Zirn<sup>109</sup> and others reported the successful use of 1 per cent sublimate of mercury, and in 1922 Fischer<sup>38</sup> reported the successful use of mercuric chloride. After the sclerosing effects of the various hypertonic solutions were reported in the early 20's and after the toxic effects of mercury had been emphasized, the solutions most commonly used were as follows:

1. The nontoxic hypertonic solutions of the various sugars and sodium chloride, the most popular of these becoming hypertonic sodium chloride, hypertonic glucose or dextrose, and mixtures of the hypertonic solutions of sodium chloride and glucose.

2. Sodium salicylate, sodium citrate, and solutions of some quinine salt, usually the hydrochloride, the latter being usually combined with urethane.

These solutions are put up by various pharmaceutical houses in various strengths and combinations and under various trade names.

The literature dealing with the use of the various solutions became enormous. In 1924 Troisier<sup>101</sup> reported using sodium citrate. In 1925 Bardy<sup>3</sup> recommended the use of quinine solution. Meisen<sup>73</sup> in 1927 recommended a mixture of sodium salicylate 25 per cent and sodium chloride 10 per cent. In the same year, McPheeters<sup>66</sup> favored 20 per cent sodium chloride. In 1928 Colt<sup>17</sup> reported the successful use of sodium salicylate with no bad results, except pain at the time of injection.

Alexander,<sup>1</sup> writing in 1926, reported good results with sodium salicylate. Schmier<sup>69</sup> in 1930 recommended sodium chloride, but warned against sloughing; in the same year Stuebner<sup>64</sup> reported excellent results using sodium salicylate. In the same year White<sup>105</sup> reported using quinine hydrochloride and urethane; Cattell<sup>13</sup> recommended quinine urethane solution in 1931, as did Lewis<sup>55</sup> in 1932, Kilbourne<sup>53</sup> in 1930, and Weeks and Mueller<sup>104</sup> in 1932.

In general the quinine urethane solution became more popular in European clinics than in American, and to a lesser extent this was true of sodium citrate and sodium salicylate. The hypertonic sugar and sodium chloride solutions and their combinations became more popular in America. These solutions were especially recommended by McPheeters<sup>66-68</sup> and De Takats<sup>26-28</sup> and many others up until fairly recently.

In general, quinine solutions have the advantage of causing a certain and very firm thrombus following the injection of a small amount of material. The disadvantages are their toxicity and the danger of sloughing when a small amount is injected outside the vein. The pain caused by their injection is also a disadvantage. This latter, however, is largely overcome by the addition of urethane to the solution. More or less the same advantages and disadvantages, each less marked, are found in the use of sodium citrate and sodium salicylate, the latter being more popular. Hypertonic sodium chloride is less efficient, apparently, as a thrombus producer than the above solutions, but is relatively nontoxic, although large doses have been followed by hematuria. Much larger amounts must be injected into the tissues to produce sloughing. It does not cause pain at the site of injection, but it does produce severe cramping pain in the extremity. Hypertonic sugar solutions are apparently still less efficient as thrombotic agents. They are nontoxic, however, may be injected into the tissues in relatively large amounts before producing a slough, and cause little or no pain at the time of injection. The higher concentrations are, however, likely to be somewhat harder to handle because of viscosity.

Various combinations of sugar and saline solutions seem to offset the disadvantages of each, but they still have the drawback of being rather inefficient as thrombus producers. Where these solutions have been used almost exclusively, occasional use of sodium citrate or quinine urethane solutions has been resorted to where the others failed to cause thrombosis (McPheeters,<sup>69</sup> De Takats<sup>28</sup>). Delater and Chailly<sup>21</sup> and Dunbar<sup>32</sup> also recommended using various solutions for different types of cases.

More recently the search for a more ideal sclerosing agent has centered mainly around the solutions of fatty acids or the salts of these acids. The most popular of these is now sodium morrhuate, usually the 5 per cent, occasionally the 10 per cent, solution. This solution was first referred to by Rogers and Murkegee<sup>80</sup> in 1919 in the treatment of leprosy, and in the same year Rogers<sup>85</sup> described its preparation. It was also used in the surgical treatment of tuberculosis. Its preparation was also described by Cutting<sup>20</sup> in 1926.

Higgins and Kittel<sup>42</sup> were the first to use sodium morrhuate in the injection treatment of varicose veins. It was further advocated as a sclerosing agent in the same year by Rogers.<sup>87</sup> In 1932 Tunick and Nach<sup>102</sup> reported 600 cases receiving injections of 5 per cent sodium morrhuate, using as a rule 2 to 5 c.c. They stated that its injection

caused no cramping pain, was the least likely of the solutions thus far used to cause sloughing, was nontoxic, and was a good thrombus producer.

In 1932 Kilbourne, Dodson, and Zeiler<sup>56</sup> published an important paper dealing with the toxicity, slough-producing properties, and bacterial action as related to phlebitis and embolism of various solutions used in the injection of varicose veins. They concluded that bichloride of mercury was too toxic; metaphane was less toxic and less likely to cause sloughing. Sodium chloride and glucose were nontoxic, relatively painless, and less likely to cause sloughing than the quinine and salicylate solutions, but they had the disadvantage of being nonbactericidal. They found sodium salicylate to be an excellent thrombus producer, but it produced cramping pain at the time of injection and was likely to produce sloughs. Lithium salicylate was painless but more toxic. They found quinine urethane excellent except for its toxicity and the danger of sloughing. They found sodium morrhuate to be nontoxic, less likely to produce serious sloughing, efficient as a thrombus producer, but having the disadvantage of being nonbactericidal.

Smith<sup>92, 93</sup> endorsed sodium morrhuate and reported more than 2,000 injections with no sloughs or other complications and a lower incidence of recurrence. Tournay<sup>99</sup> in 1933 favored the use of sodium morrhuate. However, although sodium morrhuate produced an excellent thrombus, was nontoxic, painless, and less likely to produce a slough, it was found to have one objection—some individuals were sensitive to it. Warning of the danger of this was given by Zimmerman.<sup>108</sup>

In 1934 and 1935 Ochsner and Mahorner<sup>70, 78</sup> published the results of experimental work on twenty-nine solutions. They found that sodium morrhuate injected into the veins of dogs was the most efficient thrombus-producing solution of the twenty-nine solutions tried. Sodium gyno-cardate was second. As a whole, they found sodium morrhuate Searle to be the best solution tried. In 1934 Cooper<sup>19</sup> published a report of more than 35,000 injections of various solutions in 3,164 cases. He reported 293 cases of extensive and recurrent varicose veins treated by preliminary ligation and subsequent injections. Of the various solutions he had tried, he recommended sodium morrhuate.

In 1935 Colt and others<sup>18</sup> preferred salicylate solutions and found sodium morrhuate less effective. In the same year Christie<sup>16</sup> advocated the use of quinine urethane, sodium salicylate, and 5 per cent sodium morrhuate. He issued a warning against the danger of the latter, which he stated had caused fatalities. Specific fatal cases were not, however, reported. In the same year Barker<sup>4</sup> stated that sodium morrhuate was preferred at the Mayo Clinic. Prayer and Becker<sup>52</sup> in 1935 studied the sensitization phenomena following the injection of sodium morrhuate. They reported that 7 of 175 patients receiving 783 injections of sodium morrhuate showed sensitization reactions. Probst<sup>53</sup>

in 1936 also reported several cases of sensitization reactions but no deaths following the use of sodium morrhuate. In the same year Willauer<sup>106</sup> also recommended sodium morrhuate.

Froehlich and Henrikson<sup>39</sup> in 1935 recommended sodium ricinoleate, as did Postlethwaite<sup>80</sup> the following year. They used a 2 per cent solution and found it to be effective at thrombus production and less likely to produce reactions than sodium morrhuate.

Recently Biegeleisen<sup>7</sup> has published the results of evaluating four new fatty acid solutions. He concludes: "The use of fatty acid salt solutions is an advance toward safer and more efficient sclerosing therapy." He presents four new solutions: (1) moru-quin, a loose chemical composition of sodium morrhuate and quinine, which he believes is a new and useful solution; (2) oleate quinine, combining potassium oleate and quinine, a stable mixture which he finds to have a uniform sclerosing power; (3) sylnasol, the fatty acid salt of psyllium seed oil, which he finds resembles sodium morrhuate in its action on veins; and (4) monoethanolamine oleate, a synthetic compound which he believes at present to be the most efficient sclerosing agent for the treatment of varicose veins.

Very recently Johnston,<sup>49</sup> in a paper dealing with ligation and retrograde injection, states that he uses 5 per cent sodium ricinoleate in doses of 4 to 10 c.c.

The situation in regard to solutions can be summed up as follows: As a whole the solutions of the salts of fatty acids seem to have more advantages and fewer disadvantages than any of the previous older solutions used. Of these, sodium morrhuate has been most widely used and has been found on the whole to be very satisfactory. It is perhaps more popular in America than abroad (Riddoch<sup>84</sup>). It has been shown both experimentally and clinically to be superior to other solutions, with the possible exception of sodium ricinoleate. The latter, however, has been less widely used. The newer solutions described by Biegeleisen<sup>7</sup> are extremely interesting and we hope may prove satisfactory. Certainly sodium morrhuate is not an ideal solution, but it seems to be the best that has been used so extensively. Its greatest disadvantage lies in the sensitization reactions occasionally seen. In our experience these have been extremely rare and not at all alarming. We do not believe that the disadvantage pointed out by Kilbourne and his coworkers,<sup>56</sup> namely, its not being bactericidal, should counteract other obvious advantages. Proper technique should make the danger of contamination as little as in any intravenous therapy. Proper selection of cases will largely rule out injecting veins already the site of a thrombophlebitis.

#### MOST ACCEPTABLE METHODS OF TREATMENT AT THE PRESENT TIME

The recent advances in the treatment of varicose veins of most importance have to do with various combinations of operative and injec-

tion therapy. In many therapeutic procedures no attempt has been made to correct the fundamental conditions in varicose veins. This is, in large measure, the reason for failures with the older operative procedure and the injection treatment.

The superficial veins of the lower extremity dilate because of increased pressure. This may be due to obstruction of the deep venous system, such as occurs in thrombophlebitis. In this case the dilatation is merely compensatory. This type, of course, is rarely amenable to treatment. The same thing may occur during pregnancy because of pelvic pressure obstructing the venous return from the legs. In this case the pressure, acting on veins with relatively weak walls, gradually breaks down all elasticity of the vein walls and the dilatation becomes permanent. When this occurs, the valves also become incompetent. In other cases there is no obstruction, but long periods on the feet with resulting increase in venous pressure in the lower extremities cause dilatation of the superficial venous system. An especially important factor is the inherent weakness of the veins in some individuals. Once this dilatation has gone far enough to cause the valves in the great saphenous vein to become permanently incompetent, the condition is self-propagating.

It has been pointed out by many observers that what actually occurs in the classical case of varicosities of the great saphenous system with incompetent saphenous valves is not an increase in pressure or stasis but an actual reversal in the direction of the flow.

Brodie<sup>10</sup> in 1846 described the reflux of reverse flow in the saphenous vein which occurs after emptying the vein, obstructing it, and quickly removing the obstruction. This was described by Trendelenburg some fifty-five years later and the sign given his name. Brooks<sup>11</sup> emphasized the evident actual reverse flow down the saphenous and into the deep circulation. In 1927 Berntsen<sup>2</sup> pointed out that the surgical treatment, to be effective, must keep these fundamental principles in mind. The pathology of abnormality of the venous circulation in the varicose extremity was beautifully described by De Takats, Quint, and coworkers<sup>24</sup> in 1929. Selmier<sup>50</sup> in 1930 demonstrated the reverse flow in the venous circulation by intravenous injection of substances opaque to x-rays and following their progress radiographically. This subject has been reviewed comprehensively by McPheeters.<sup>68</sup>

It would seem fairly obvious that if a saphenous vein were dilated and its valves incompetent, and one injected or excised the varicosities below the knee, regardless of how well this were done, one would get subsequent dilatation of other veins emptying into the saphenous. One cannot remove, nor is it desirable to remove, all the superficial venous system of the leg. As long as there are any veins, no matter how small, which communicate with a larger vein having increased venous pressure, they will dilate and become varicosities.



This does not apply only to varicosities of the great saphenous system, but these are the most frequent and most typical. The same principle applies to varicosities of the small saphenous vein. This vein occasionally empties into the great saphenous and the two systems become one. More frequently it empties into the deep circulation near the popliteal space. If the valves in this communication are incompetent, the same reverse flow occurs. In any group of varicosities communicating with the deeper circulation through a dilated channel with incompetent valves, the same principle holds.

It is well known and has been shown histologically that after the formation of even the firmest thrombus by injection there is some retraction of the thrombus and recanalization. Obviously, if these small veins within veins are connected with a large vein in which there is an increased pressure of reverse flow, they will eventually dilate and the varicosities will recur.

Lufkin and McPheters<sup>62, 69</sup> and others pointed out this retraction and recanalization. McAnsland<sup>64</sup> points out that no treatment cures the tendency toward the development of varicose veins. Hence, failures are not necessarily recurrences of persisting varices, but they may be the formation of new ones.

This recanalization does not depend upon the solutions used. Quinine and urethane solution has always been considered an efficient thrombus producer, yet Faxon<sup>35</sup> reported 63 per cent of recurrences after the use of this solution; Howard<sup>48</sup> reports 100 per cent recanalization. It seems probable that the rôle of recanalization in recurrence of varicosities has been overemphasized and the formation of varicosities from previously uninvolved veins not sufficiently emphasized. Even when using the now more or less standard technique of injection, one of the better solutions and properly selected cases, the injection treatment when carried out alone often yields very disappointing results from the standpoint of recurrence. In an attempt to overcome this deficiency, various types of operations combined with injection have been used during the past several years.

For a period of between two and three years, beginning in 1930, the favored procedure in the treatment of varicose veins in the Vanderbilt University Hospital was the complete removal of the saphenous vein, followed by injection of varicosities below the knee. This procedure was carried out in all cases where incompetence of the saphenous valves with backflow in this vein was demonstrated. The vein was divided at its junction with the femoral after dissecting out and dividing the higher branches. It was then stripped out with a Mayo vein stripper as far as possible, usually to a point slightly below the knee. Varicosities of the leg were later obliterated by injection. The number of cases treated in this manner was relatively small, but the results were highly satisfac-

tory. This type of treatment has been for the most part discarded in favor of the simpler procedure of ligation of the saphenous followed by injection of the varicosities.

Ligation of the saphenous vein in conjunction with injection was first carried out and reported by Tavel<sup>96</sup> in 1904. He ligated the saphenous vein and injected 5 per cent carbolic acid below the ligation. Thus not only was he the first to combine ligation and injection, but he was also the first to carry out what we now know as retrograde injection, which will be considered later.

To De Takats<sup>27</sup> goes the credit for emphasizing the importance of high ligation of the saphenous vein and its popularization. He first advocated this as an ambulatory procedure to be used in conjunction with injection of varicose veins in 1930. He stated that it would definitely decrease the danger of embolus after injection and obliteration of the saphenous vein. He also repeatedly pointed out its usefulness in breaking dependably and permanently the vicious cycle of reverse circulation and removing the head of pressure from the saphenous tributaries. He<sup>27</sup> recorded that 22 to 72 per cent of recurrences followed the Trendelenburg operation, but he believed the results would be excellent if combined with obliteration by injection. However, the reason that the Trendelenburg operation was not more satisfactory was probably due to the fact that it was not sufficiently high, the ligation being carried out usually below the first branches of the saphenous vein. The importance of the high interruption of the saphenous vein has been pointed out repeatedly by Homans<sup>44-47</sup> in connection with operative treatment of varicose veins. It is probably even more important when simple ligation or division between ligatures is carried out in conjunction with injection. This has been pointed out by De Takats and his coworkers,<sup>27, 28, 30</sup> Hawkes and Borsher,<sup>41</sup> Howard,<sup>48</sup> Edwards,<sup>33</sup> Willauer,<sup>106</sup> and others.

In cases of marked varicosities of the saphenous system, the saphenous vein itself may not be the only incompetent communication with the deeper circulation. The communicating vein of the small saphenous may be at fault. Occasionally there is a large communicating vein with incompetent valves at about the junction of the middle and lower thirds of the saphenous vein.

In general, if the valves of the great saphenous vein are not competent, only injection is carried out. This is probably the cause for many recurrences. De Takats<sup>27</sup> in 1930 stated that he advocated operating radically on 4 per cent of cases with incompetent communicating veins. Other men, among them Willauer,<sup>106</sup> have stressed the advisability of ligating the small saphenous vein at its junction with the popliteal when this system is involved. Other communicating veins, such as the one mentioned above, should be ligated when at fault. The detection of these communications which should be obstructed has been emphasized and made easier by the multiple tourniquet test devised by Mahorner and Oelsner.<sup>71</sup>

It would seem that ligation has the advantage over stripping out of the saphenous vein, being a much more minor procedure. Removal of the saphenous vein, requiring longer hospitalization, is usually performed under general anesthesia and opens up a wide field to bacterial invasion. Undoubtedly the danger of anastomosis around a ligature and recurrence is greater after ligation than after extirpation of the entire saphenous vein. It is, however, doubtful if it is justified in most cases. Until recently, however, we felt that it should be carried out in a few particularly recurrent cases.

Perhaps the most valuable recent contribution to the therapy of varicose veins is the introduction of so-called retrograde injection. It seems at the present to combine the advantages of extirpation of the saphenous vein and simple ligation and not to have many of the disadvantages of either procedure. As previously mentioned, Tavel<sup>96</sup> was the first to carry out retrograde injection. It was more recently introduced, in 1927, by Moszkowicz.<sup>76</sup> To Faxon<sup>36</sup> should go the credit for introducing it into this country and aptly emphasizing its advantages. It has also been recommended by Fantus,<sup>34</sup> Swinton,<sup>95</sup> Haggard and Kirtley,<sup>40</sup> and very recently Johnston.<sup>49</sup> The procedure consists simply of division between ligatures of the saphenous vein at its junction with the femoral. Into the distal stump a sclerosing solution is then injected. As pointed out by Johnston, the obliteration of the entire saphenous vein, which is accomplished by this method, should result in fewer recurrences than simple ligation of the vein followed by injection from below. The mortality or morbidity should not be increased over that of simple ligation.

At the present time the most satisfactory procedures to be carried out in the treatment of varicose veins are as follows: Simple injection should be carried out in isolated varicosities without demonstrable incompetent communications with the deep circulation. In cases of incompetent saphenous valves, the saphenous vein should be divided between ligatures at its junction with the femoral, after dissecting out and dividing between ligatures all of the upper branches. This is to be followed by retrograde injection. In all cases, careful search for other incompetent communicating veins should be made. If these are found, they should be divided between ligatures at their source and retrograde injection carried out from this point.

Somewhat special groups of patients with varicose veins may call for some modification of this treatment.

One of the most frequent types of patient to seek relief from varicose veins is the pregnant woman. Pregnancy is one of the most common causes of the development of permanent varicosities, and frequently varicosities are the chief source of suffering during pregnancy. The knowledge that varicosities can be treated by injection during pregnancy is not new. McPheeters<sup>69</sup> has long advocated such treatment,

as have De Takats<sup>26, 27</sup> and others. Treatment of varicosities in this type of case, however, apparently needs emphasis.

As late as 1935, Cheatham and Peck<sup>15</sup> stated that the idea is still not prevalent that such varicosities should be treated. They pointed out that the textbooks of both DeLee and Williams state that little can be done for varicosities during pregnancy.

For several years we have made it a practice to treat varicose veins during pregnancy, up to about the seventh month, much as we treat varicose veins in any other case. If ligation is indicated, this is carried out. After ligation or if it is not necessary, the larger and more troublesome veins are obliterated by injection. More recently we have employed retrograde injection in these as in other patients. No complications have occurred to date. We are, however, less assiduous in attempting to obliterate all dilated veins. Except when treated very early in pregnancy, only the ones causing symptoms are obliterated. The patient returns six to eight weeks after delivery for further treatment. Usually, if ligation has been done, the smaller varicosities, and many times the larger ones, will entirely disappear after delivery.

A number of patients have been observed during pregnancy who had previously had high saphenous ligation either during or between former pregnancies. These patients, of course, have the same amount of venous obstruction acting as a causative agent as previously. They do not, however, develop varicosities of the saphenous system. They frequently do develop varicosities of the upper thigh, particularly of the posterior surface; these veins anastomose with veins above the saphenous and femoral junction, very frequently the gluteal veins. If these varicosities cause symptoms, they should be injected. Labial varicosities can be injected. It is, however, a somewhat more difficult procedure and in our experience only rarely necessary or desirable.

Another special group of cases is that group in which varicosities occur in the very old or infirm. Usually only the injection treatment is carried out in these patients, and this is confined to the larger varicosities. If they recur, they may be re-injected.

#### TECHNIQUE

So far we have not discussed the technique of any therapeutic procedure in detail. This has been covered very well indeed by many authors. In those cases where it may still seem advantageous to extirpate the entire saphenous vein, it is best removed by stripping operation, using the Mayo vein stripper. The most important details include extraordinary care in regard to asepsis and hemostasis. One should be certain of dividing the vein at its junction with the femoral and should dissect out and divide all of the upper branches.

Formerly it was believed that the sclerosing solution should ideally be injected into a vein as nearly empty as possible, and immediately

after injection the vein should be maintained in this collapsed state by a supporting bandage or dressing. This it was hoped would cause the vein walls to unite more or less directly by fibrosis with the maximum obliteration and minimum thrombus formation. It is also true that a better obliteration results if the solution reaches the vein in high concentration, thus assuring more damage to the intima. With this in view, various methods of occluding portions of a vein from the surrounding ones were devised. In the case of the long varicosities, a segment between two tourniquets was injected, only one injection being made if one of the toxic solutions were used. In the case of the hypertonic sugar and salt solutions, multiple injections were made between many tourniquets applied simultaneously, as described by McPheeters.<sup>69</sup> For more isolated superficial veins, various types of occluders were devised to keep the solutions localized longer (McPheeters,<sup>69</sup> Potts,<sup>81</sup> Theis<sup>98</sup>). Because a sclerosing solution reaches the intima in a higher concentration if the vein is empty, injection in the horizontal position has been most popular. For this reason various methods have been devised to enable the needle to enter a full vein and to enable the injection to be made into an empty one. Occluders, tourniquets, and special tables, such as the one devised by Stuebner,<sup>94</sup> were used for this purpose.

It is no longer held that veins should be kept collapsed after injection. In fact a better obliteration follows a full thrombus (McPheeters<sup>69</sup>). The wearing of some light supporting bandage after injection, however, makes the patient distinctly more comfortable.

The value of limiting the sclerosing solution to a given area was especially useful when using the glucose saline solutions. The sclerosing power of these solutions was their weakest point. This is not necessary with sodium morrhuate. We still prefer to inject varicose veins with the patient lying down; in many clinics they are injected with the patient standing. We use no tourniquets, constrictors, etc., preferring that the solution go as far as possible and the maximum extent of the thrombosis be obtained. The special equipment needed includes Luer lock syringes or syringes of some similar type, usually 5 and 10 c.c., and several sizes of needles with short bevels. It is a mistake to use too small a needle, as this slows up injection and causes unnecessary dilution of the solution.

Very small cutaneous veins, so-called spiders or sunbursts, can be effectively obliterated by using a very small needle and by injecting a very small amount of fluid, preferably 5 per cent sodium morrhuate (Biegeleisen<sup>6</sup>). The very small ones may be obliterated with somewhat less danger of slough by injecting small amounts of sodium morrhuate mixed with air, i.e., bubbles or even small amounts of air.

The technique of saphenous ligation has been especially described by De Takats<sup>27, 30</sup> and Faxon,<sup>36</sup> the most important points being the use

of local anesthesia, strict attention to asepsis and hemostasis, and careful dissection to insure ligation above the three upper branches: the superficial iliac circumflex, the superficial epigastric, and the external pudendal. Recently Johnston<sup>49</sup> has pointed out the advisability of carefully dissecting out and dividing these branches. Their position is variable and unless this is done they may be missed. This is particularly true in the occasional cases where they actually empty directly into the femoral vein.

We agree with Faxon<sup>36</sup> that the operation is not trivial and prefer always to hospitalize a patient for twenty-four to forty-eight hours for this operation. This is largely due to fear of infection. The incision is made in a region requiring special cleansing of the skin. An infection at the fossa ovalis is indeed a serious thing. An added risk is due to the fact that so many of these patients have had varicose ulcers with residual infection in the lymph nodes which lie in the operative field.

The technique of division of the saphenous vein and retrograde injection has been very adequately described by Faxon<sup>36</sup> and very recently by Johnston.<sup>49</sup> The vein is divided between ligatures as in simple ligation. The sclerosing solution is then injected into the distal stump. We have seen no necessity for using cannulas as described by the above authors. An ordinary syringe with a fairly large needle suffices. Both ends are ligated with suture or transfixion ligatures. If any of the sclerosing solution has been spilled, the wound should be gently flushed out with salt solution. The wound is closed without drainage with interrupted silk sutures. Johnston has pointed out the danger of contamination of these wounds. For this reason we use a very fine enteleular skin suture of fine silk. The wounds are then covered with silver foil as an added protection and a very tight outer dressing applied. If 5 per cent sodium morrhuate is used, as much as 10 c.c. may be injected into a saphenous vein without undue reaction. In cases of extensive thrombosis with considerable local reaction, the patients are made more comfortable by wearing light elastic bandages for a few days over the thrombosed veins. The patients are encouraged, but not forced, to walk.

#### CONTRAINDICATIONS TO TREATMENT

All operative procedures may be contraindicated because of advanced debilitation or senility. Extreme disability should also be a contraindication to extensive injection treatment. It is sometimes justifiable, however, to obliterate those veins directly causing symptoms. This is particularly true in the case of ulcers. These may often be healed, at least for some time, by simply injecting the vein or veins in the vicinity of the ulcer.

The chief contraindication to any type of therapy is, of course, thrombophlebitis. If the deep circulation has been the site of extensive thrombophlebitis in the past, it is unlikely that the patient will be bene-

after injection the vein should be maintained in this collapsed state by a supporting bandage or dressing. This it was hoped would cause the vein walls to unite more or less directly by fibrosis with the maximum obliteration and minimum thrombus formation. It is also true that a better obliteration results if the solution reaches the vein in high concentration, thus assuring more damage to the intima. With this in view, various methods of occluding portions of a vein from the surrounding ones were devised. In the case of the long varicosities, a segment between two tourniquets was injected, only one injection being made if one of the toxic solutions were used. In the case of the hypertonic sugar and salt solutions, multiple injections were made between many tourniquets applied simultaneously, as described by McPheeters.<sup>69</sup> For more isolated superficial veins, various types of occluders were devised to keep the solutions localized longer (McPheeters,<sup>69</sup> Potts,<sup>81</sup> Theis<sup>98</sup>). Because a sclerosing solution reaches the intima in a higher concentration if the vein is empty, injection in the horizontal position has been most popular. For this reason various methods have been devised to enable the needle to enter a full vein and to enable the injection to be made into an empty one. Occluders, tourniquets, and special tables, such as the one devised by Stuebner,<sup>94</sup> were used for this purpose.

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The technique of saphenous ligation has been especially described by De Takats<sup>27, 30</sup> and Faxon,<sup>30</sup> the most important points being the use

As previously stated, the immediate results of the injection treatment seemed excellent; that is, the veins were quickly and efficiently thrombosed and obliterated and the patients were relieved of their symptoms. With the development of better technique and more satisfactory solutions, the danger of toxic reactions and the frequency of sloughs also diminished. The danger of embolism, however, was still feared.

At the first glance it would seem that the production of a massive venous thrombosis would result in an occasional embolic death. This is the case, of course, in the ordinary septic thrombophlebitis. In the case of injection obliteration of varicosities, however, the facts have been proved otherwise. Statistics show that there is very little danger of embolism following the injection treatment of varicose veins. Histologic studies on veins following injection show the reason for this.

In spite of the fact that there was a gradual increase in the number of cases of injection recorded, the fatalities were few, so that it would seem apparent that the danger was slight; and when actual comparisons were made, it was found to be less than following operative treatment. Bardy<sup>3</sup> in 1925 stated that operative therapy was satisfactory but that the danger from embolus was greater than with injection. In the same year Dunbar<sup>32</sup> stated that there was more danger of embolism following operation than following injection, although in both instances the results were satisfactory.

In 1927 Meisen<sup>73</sup> reported 500 cases treated with 2,224 injections without any deaths. In the same year McPheeters<sup>66</sup> reported 31 cases with 180 injections without complications and stated that the mortality was lower than with operation. In the following year McPheeters<sup>67</sup> collected a series of 53,000 injections with 7 deaths, a mortality of 0.033 per cent. In the following year De Takats<sup>25</sup> reported 1,000 injections without a death and emphasized the low mortality of the method. Kilbourne,<sup>53</sup> in 1929, also reported that in a series of 4,607 cases operated upon there was 1 death from embolism in every 250 cases. In 1930 Pennoyer<sup>79</sup> found 4 authentic cases of death from pulmonary embolism in 400,000 reported injections. In 1932 Lewis<sup>59</sup> reported 848 cases receiving 3,532 injections with no deaths. In 1934 Kilbourne<sup>57</sup> reported 20,000 injections with no mortality. He studied 20 reported deaths after injection and concluded that the majority were due to bacteremia caused by contamination at the time of injection or the lighting up of an old thrombophlebitis. These factors can be eliminated by proper technique and proper selection of cases. De Takats<sup>29</sup> also believes that injection of veins in patients who have previously had thrombophlebitis is the most important factor in the formation of emboli and death.

It is also interesting that Kilbourne<sup>57</sup> points out in this connection that there is less danger of infection developing after the use of solutions which are definitely bactericidal. Most of the solutions now in use are



fited by any therapy, and great harm may be done. In addition, if injection is carried out, the inflammatory process may be activated, the process spread, and embolism may occur (De Takats<sup>29</sup>). The latter is true of phlebitis confined to the superficial system as well as to thrombophlebitis of the deep veins. Varicosities often become the site of a spontaneous thrombophlebitis. Zimmernan<sup>108</sup> mentions a case of thromboangiitis obliterans activated by injection. Certainly no patient with impaired arterial circulation in the extremities should have varicosities obliterated.

One of the greatest drawbacks to the injection treatment of varicose veins is the ease with which it is carried out. It is used by many without sufficient understanding of the disease, proper examination of the patient, or proper selection of cases. Although the technique of injection is simple, accidents may occur in inexperienced hands. Large sloughs from fluids injected outside of the vein are the most common complications. We have observed one patient with gangrene of the distal portion of the foot following accidental injection of the anterior tibial artery.

#### RESULTS OBTAINED

It may be stated briefly that the earlier operative procedures were relatively unsuccessful. Later the complete extirpation of the saphenous vein and the varicosities below the knee gave excellent results. This operation, however, was of too great a magnitude for the disease. This was especially true from an economic standpoint, the treatment requiring relatively long hospitalization following a major operation.

The early reports of the injection treatment were almost universally favorable. Subsequently when the more irritating and toxic solutions were used, there were many reports of complications, such as sloughs and pain; even an occasional death was reported. With more innocuous solutions coming into use again, the only complication reported was sloughing.

Cattell<sup>12</sup> also discussed and reported such complications as burning after injection, nausea, and sloughing. Schmier<sup>39</sup> warns against the danger of slough. Kilbourne<sup>54-56</sup> also discusses the treatment of post-injection sloughs and other complications; he emphasizes the importance of reporting complications in order that the real dangers of this form of treatment may be understood.

In 1931 De Takats<sup>28</sup> pointed out the danger of toxic solutions, such as mercury, the salicylates, and quinine. The following year<sup>29</sup> he warned against injecting veins that are at the time or have been in the past the site of thrombophlebitis. Colt,<sup>17</sup> in his article dealing with the history of the evolution of injection treatment of varicose veins, also emphasizes the complications following the employment of the more toxic and irritating solutions.

especially using the earlier and more irritating solutions, resulted practically always in thrombosis and rapid obliteration of the veins. After a large number of patients had been treated and followed in some clinics over a period of time, however, reports as to the results became very variable, ranging from the usual optimistic to those frankly pessimistic. In Meisen's<sup>73</sup> 500 cases there were 14 recurrent cases which had been operated upon and 10 recurrent cases in an additional series of 50 cases; thus 24 cases were recurrences following previous operation. He believes the rate of recurrence to be lower after the injection treatment. De Takats<sup>28</sup> in 1931 reported 10 per cent recurrences. Kettel<sup>52</sup> in 1932 reported 400 cases with 94.5 per cent immediate cures and 91.5 per cent cures after one year. One-third of the latter group showed some recurrences without symptoms. In 1932 Lewis<sup>59</sup> stated that recurrences were infrequent and pointed out that recurrences and the formation of new varicosities should not be confused. In the same year Wymer<sup>107</sup> emphasized the relative infrequency of recurrences after injection treatment. In 1933 De Tarnowsky<sup>31</sup> reported 63 per cent cured. In the same year Faxon<sup>35</sup> at the other extreme reported 63 per cent recurrences in 1.4 years. The following year McKinstry,<sup>65</sup> in reviewing the work for the previous year, 1933, commented upon the marked variations in the reports as far as results were concerned and the inadequacy of our knowledge of the subject.

All of the above results apply to cases treated with injection alone. It is believed at the present time that these results are being greatly improved upon by combining obstruction of communications with the deep circulation with obliteration by injection.

As stated previously, our own results combining extirpation of the saphenous vein with injection were excellent. Recently we have tried to trace all of the patients treated in this manner. Most of them were treated between four and five years ago. Many of them have not been traced to date. There have been no recurrences in the ones examined which were marked enough to cause symptoms or to demand re-injection.

In 1933 De Takats and Quillin<sup>30</sup> reported 170 recurrences in patients treated with combined ligation and injection. Hawkes and Borsher<sup>41</sup> stated that injection combined with ligation in the lower or midportion of the thigh had been followed by recurrence, but they had no recurrences in 10 cases where high or fossa ovalis ligation was carried out. Howard<sup>45</sup> in 1934 reported his results one year and twenty-nine months after treatment by combined ligation and injection. He found there was some recanalization, but that 77 per cent were cosmetically cured; he believed the best results were obtained by this treatment. In the same year Edwards<sup>33</sup> reported excellent results and fewer injections necessary after high ligation of the saphenous vein. In 1935 Ferguson<sup>37</sup> advocated combined ligation and injection, reporting good results and no complications.

only weakly or not at all bactericidal. This should not be of importance, since injections should not be carried out if dependence on asepsis must rest with the bactericidal power of the solutions used. In 1935 Theis<sup>98</sup> reported 14,000 injections in 882 patients with 1 fatal pulmonary embolism.

The reasons for the relative safety of the injection method are explained by histologic and pathologic findings. When any of the common operative procedures for treating varicose veins are carried out, blood clots are left in close proximity to open veins and ligated veins form thrombi in their stumps. These are fairly firm clots but they are not dependent on injury to intima for their formation. In postoperative thrombophlebitis, simple stagnation of blood is probably the most important factor. Hence the thrombus is not densely adherent to the intima and therefore at times is loosened into the blood stream. In the case of bacterial thrombophlebitis this danger is much greater. The thrombus is formed by the action of the bacteria on the stagnant blood stream and upon the intima. After the formation of this thrombus, however, the bacterial action is to break down and liquefy it, thus replacing the original and rather firm clot with a mass of small thrombi, loosely adherent in a semifluid state. This furnishes the ideal basis for embolism.

In the case of thrombosis of a vein following the injection of some highly irritating substance, the thrombus forms as a result of severe injury to the intima. The intimal cells first swell and often rupture; the thrombosis is laid down upon this injured area and becomes densely adherent to it. Instead of subsequent liquefaction, the thrombus quickly undergoes organization, the fibroblasts growing directly from the vein wall into the clot. Thus there is less danger of emboli breaking off and entering the blood stream.

In 1894 Delore,<sup>22</sup> in defending the treatment of varicose veins by injection of iodotannic solution, pointed out that the resulting condition was a chemical endophlebitis and that the thrombus depended on this. Since that time, histologic studies, both on the veins of experimental animals after injection and on the veins of patients excised after injection, have been carried out by various workers. All show the same type of thrombus following injury to the intima, resulting in fibrosis of the clot and vein wall. The following have contributed to this important phase in understanding the injection treatment of varicose veins: Nicholson,<sup>77</sup> Lehman,<sup>58</sup> De Takats,<sup>25, 27</sup> Lufkin and McPheeters,<sup>62</sup> McPheeters,<sup>69</sup> and Mahorner and Oehsner.<sup>70, 78</sup>

With a fairly definite understanding as to the comparatively slight risks involved in the injection treatment, the next most important consideration naturally was and is that of results from the standpoint of cure and relief of symptoms. As stated previously, most of the earlier reports were optimistic. In most hands the injection of varicose veins,

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Retrograde injection has not been in use a sufficient length of time for the later results to be known. The immediate results in our own cases have been excellent. We have no complications with this method. All the patients have had their period of treatment shortened because of the fewer number of subsequent injections required. Some of these patients have not required any further injections, all varices being obliterated by the retrograde injection. Faxon,<sup>36</sup> Haggard and Kirtley,<sup>40</sup> and Johnston<sup>49</sup> have also reported good immediate results.

#### SUMMARY AND CONCLUSIONS

In summary, it may be said that the modern or present-day treatment of varicose veins consists primarily of occluding them by the injection of sclerosing solutions. The combination of this method with ligation of the saphenous or incompetent communicating veins, where indicated, is the treatment of choice. We believe that the method of retrograde injection is of great help in carrying out this treatment. At present, 5 per cent sodium morrhuate seems to be the solution of choice. Other solutions of fatty acid salts or these salts combined with some other compound may prove to be superior.

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Dr. Waltman Walters, Dr. Hugh Cabot, and Dr. James T. Priestley, of Rochester, Minn., reported on 46 plastic operations, chiefly lateral pelvioureterostomy, and division and reimplantation of the ureter, for the same condition; 15 of these subsequently required nephrectomy; 33 patients were cured or improved. Most of the secondary nephrectomies were done early in their experience; they attribute the recent improvement in results to the use of temporary nephrostomy following the plastic procedure.

Dr. William C. Quinby, of Boston, and Dr. James C. Sargent, of Milwaukee, both obtained favorable results with section and reimplantation of the ureter (Kuster's operation), the former having several patients well more than ten years after operation.

Dr. Nelse F. Ockerblad and Dr. Hjalmar E. Carlson, of Kansas City, described the distribution of ureteral pain as determined by stimulation of the ureter through a catheter electrode. They believe that the typical location of ureteral pain is a great aid in distinguishing lesions of the ureter from intraperitoneal disease.

Dr. J. Duane Miller and Dr. William J. Butler of Grand Rapids, Mich., stated that cystograms and urethragrams are of great value in determining the cause of urinary incontinence in the female, and that they serve as valuable guides to the type of repair required.

Dr. George M. Fister, of Ogden, Utah, drew an analogy between interstitial cystitis (Hunner ulcer) and lupus erythematosus, and reported a case in which great benefit had followed the parenteral injection of preparations of bismuth and of gold sodium thiosulphate. Any useful addition to the therapy of this most troublesome condition will be warmly welcomed.

Dr. C. D. Creevy, of Minneapolis, concluded that the factor which makes emptying of the chronically distended bladder potentially dangerous is not, as is commonly claimed, the rate at which the urine is withdrawn, but rather the introduction of infection by the catheter; he supported this contention by autopsy records, showing that patients whose bladders were emptied suddenly died of infection, and that the rate of emptying the bladder did not influence either the pathologic picture in fatal cases or the mortality in all cases. Gradual emptying of the bladder should be replaced by aseptic catheterization.

The second morning was given over to a symposium on renal tumors starting with an historical review by Dr. Judson Bennett Gilbert, of Shenectady.

Dr. E. T. Bell, of Minneapolis, presented a sample and logical classification of renal tumors.

Calcification in renal neoplasms was described by Dr. George F. Cahill, of New York, in 15 per cent of 84 renal neoplasms. It is usually secondary to hemorrhage or necrosis and is often associated with or followed by dissemination of the tumor.

Dr. Walter H. McNeill, Jr., of New York, reported a case of Wilms' tumor of the kidney treated by x-ray alone (10,000 R. over a period of more than a year), with apparent recovery at the present time. He cited the case of Coley and Ritchey who was well three years after irradiation alone, but concluded that the best prognosis is afforded by irradiation followed by nephrectomy.

Dr. Archie L. Dean, of New York, said that renal tumors in the adult are radioresistant as far as the possibility of cure is concerned, but that many are radiosensitive in that they may diminish materially in size after irradiation. It is to be remembered that irradiation injures the walls of the blood vessels in the tumor and may lead to infarction and severe bleeding. Preoperative irradiation



# Review of Recent Meetings

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## REVIEW OF THE THIRTY-FOURTH ANNUAL MEETING OF THE AMERICAN UROLOGICAL ASSOCIATION, MINNEAPOLIS, MINN., JUNE 28-JULY 1, 1937

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**A**TTEENDANCE at the meeting was unusually large considering its location in the Middle-West (856 registering). A feature of the meeting was the largest scientific exhibit in the history of the Association, more than sixty exhibits being presented.

The first half day was devoted to a symposium on hydronephrosis. The common extrinsic causes thereof were enumerated by Dr. Ray M. Bobbitt, of Seattle, who feels that accessory vessels to the lower pole of the kidney cause obstruction only if accompanied by periureteral fibrosis or ptosis. Dr. C. P. Mathe, of San Francisco, discussed intrinsic causes, grouping them as congenital, acquired, and traumatic.

Dr. E. G. Crabtree, of Boston, summarized current knowledge of hydronephrosis of pregnancy. He stated that the underlying cause is compression of the ureters by the enlarging uterus, but that this effect is intensified by some endocrine factor which diminishes the tone of the renal pelvis and ureters; and he reviewed the experimental evidence supporting this contention. Regression ordinarily begins three weeks after delivery and is complete in seven weeks.

Dr. Roy B. Henline and Dr. James L. Bray, of New York, advocated the use of serial retrograde pyelograms to determine the emptying time of the renal pelvis in the presence of questionable hydronephrosis; a kidney requiring more than ten minutes to expel the contrast medium is regarded as abnormal.

The next four papers reflected the increasing optimism with which operations for the relief of obstruction at the ureteropelvic junction are now regarded. Although the first such operation was performed by Trendelenburg in 1886, most surgeons are still inclined to remove kidneys which have become hydronephrotic as the result of obstruction from accessory renal vessels, periureteral fibrosis, and stricture.

Dr. Samuel Lubash, of New York, described a modification of Kuster's division and reimplantation of the ureter which has worked well in the experimental animal and in one human case.

Dr. Frederick E. B. Foley, of St. Paul, reported his experience in 20 operations in 19 cases with his Y-plasty, in which he takes a triangular flap from the inferior surface of the renal pelvis, draws it into a vertical incision in the lateral wall of the ureter, and pulls the junction into a dependent position. Accurate suture is most important. He reviewed 20 operations on 19 patients with almost uniformly good results; all had been followed for considerable periods by means of retrograde pyelograms. This procedure is theoretically superior to previous methods in that it neither interrupts the continuity of the pelvis and ureter nor causes buckling at the site of repair.

Dr. Norris J. Heckel and Willard O. Thompson, of Chicago, reported their very interesting experiences with the use of anterior pituitary-like substance for undescended testis in 28 patients. Descent under treatment occurred in 25 per cent, all of whom were under thirteen years of age. Failures were found at operation to be due to abnormalities of the structures surrounding the testis.

Most interesting was their observation of enlargement of the genitals which was just noticeable in 4 and very evident in 11 patients. The enlargement appeared only after nine or more weeks of treatment with a dosage varying from 100 to 1,000 units three to six times weekly.

The authors suggest that this regime may prove useful as a preliminary to orchidopexy, to supplement unsuccessful operation, enlarge the penis before operation for hypospadias, and in Fröhlich's syndrome (the genitals increased in size in 9 of their 12 cases of this type).

Dr. Charles B. Huggins, of Chicago, treated spermatocele in 9 elderly men with x-ray with success. He cautioned against its use in young men, and shielded the other testis with lead during treatment.

Dr. G. R. Livermore, of Memphis, treats hydrocele by aspiration with a trocar through which linen tape soaked in sodium morrhuate is then introduced; 15 out of 16 cases were cured.

Dr. Grayson Carroll, Dr. Bransford Lewis, and Dr. Louis Kappel, St. Louis, found by in vitro experiments that mandelic acid can kill *B. proteus* and *Eschericia coli*, while aerogenes and pyocyanus survive even the "optimum" pH of five and concentration of 1 per cent. They claimed that 72 per cent of all cases treated with mandelic acid were cured.

Dr. Russell Herrold, of Chicago, reported that sulfanilamide (prontylin), although it failed in vitro to kill *Eschericia coli* in a concentration of 1 in 120, nevertheless cured 75 per cent of infections in the bladder and kidneys. It was ineffective in the presence of urinary stasis and calculi. Moderate reactions were frequent but not serious. He regards it as a "helpful adjunct" in chronic pyogenic prostatitis. It is his initial impression that sulfanilamide is a more effective urinary antiseptic than is mandelic acid.

The symposium on pyogenic prostatitis was not productive of any new data.

Dr. J. Sidney Ritter and Dr. Charles Lippow, of New York, made histologic studies of the prostates of guinea pigs and humans after the infection of electargol as advocated by McCarthy. They, unlike O'Connor, saw no evidence of untoward effects.

Dr. Robert E. Cumming, of Detroit, is skeptical of the value of massage, heat, and intraprostatic injections. He recommends neosarsphenamine and antistaphylococci serum for infections with staphylococci, and sulfanilamide for streptococci. When these measures were preceded by the eradication of other foci of infection, 75 per cent of his patients were relieved.

Dr. Henry A. Kreutzmann, of San Francisco, made cultures from the lumen of the vas deferens and found them positive in 40 per cent of patients with chronic prostatitis, cystitis, and in those recently subjected to urethral instrumentation.

These findings corroborate the popular idea that the epididymis becomes infected from the prostate by way of the lumen of the vas deferens.

Dr. Owsley Grant, of Louisville, discussed the treatment of "resistant" chronic prostatitis by the intraprostatic injection of 1 per cent mercurochrome, a measure with which he is very favorably impressed.

may reduce the size of a tumor but will not make operable a tumor which is inoperable because of local extension or metastasis. Technique was discussed.

Dr. George Gilbert Smith, of Boston, discussed the surgery of renal neoplasms. He employs a lumbar incision for small tumors and for those of uncertain nature. The transperitoneal approach is used for large growths because it permits earlier control of the blood supply and thus lessens hemorrhage at operation.

The second afternoon was occupied by the presidential address and the Guitoras lecture. Dr. Gilbert Thomas, of Minneapolis, the president, reported the results of a study of a large series of cases of renal tuberculosis; he took the position that renal tuberculosis is a slowly progressing disorder in the treatment of which conservatism is essential. It is advisable to treat the tuberculosis with general hygienic measures, meanwhile taking as long a time as is necessary to determine the condition of the other kidney; when it has been shown to be free of disease, the tuberculous kidney should be removed.

Occasionally, under hygienic measures alone, a minimal renal tuberculosis appears to heal with the disappearance of bacilli from the urine; bilateral disease may so improve as to permit the patient to return to work.

In the man, however, unilateral destructive lesions require surgery after deliberate rather than hasty study.

Dr. W. F. Braasch, of Rochester, Minn., in the Guitoras lecture made an exhaustive review of pyelonephritis. He emphasized the frequency of the colon bacillus as the primary invader and the importance of stasis as a predisposing factor, and pointed out that infection may lead to stasis by producing toxic atony, and later fibrosis of the renal pelvis and ureter.

He discussed the relationship of infection, especially with staphylococci, to stone formation. Retrograde pyelography is of great value in identifying the cicatricial changes of pyelonephritis and the destructive lesions of tuberculosis.

Modern conceptions of chemotherapy were described, with special emphasis upon the value of the ketogenic diet and of mandelic acid in bacillary infections; of neoarsphenamine in lesions due to cocci, and of sulfanilamide in the presence of gram negative bacilli, *B. proteus*, streptococci (except *S. fecalis*), and staphylococci. While this last agent is still undergoing intensive study, there seems to be definite evidence of its value. The need for eliminating stasis cannot be forgotten in dealing with resistant infections.

On the last day, Dr. O. A. Nelson, of Seattle, called attention to the frequency with which chronic infection of the uterine cervix produces urinary frequency. Granular urethritis is usually found. In his 87 cases, cauterization of the cervix done in 43 failed to relieve the symptoms. In 36 cases, the Sturmdorf operation was done, with 8 failures.

This method ought to be borne in mind in those patients whose granular urethritis is not relieved by ordinary methods (dilation, topical applications, heat).

Dr. William M. Coppridge, of Durham, N. C., reported a case of spontaneous subcapsular hematoma. This rare condition was recognized by Willis in 1700. In the acute form there is pain in the renal area with the formation of a mass and evidence of internal hemorrhage. In the chronic form a painless mass is associated with secondary anemia. Nephrectomy is often required. Microscopic examination oftenest shows chronic glomerulonephritis.

Dr. Richard Chute and Dr. Sylvester Kolley, of Boston, called attention to the frequency with which lesions of the kidney and ureter reproduce the symptoms and findings of gastrointestinal disorders, particularly appendicitis; and they recommended careful urographic study whenever there is anything atypical about the symptoms or findings in what appears to be gastrointestinal disease.

pathologic and scar tissues are removed. Following this a graft or pedicle is used. If a graft is used, full thickness is advocated. If a flap is the choice, it may be taken from any one of a number of places; arm, chest, or back. Frequently a graft from the forehead is brought down to the tip of the nose, but this leaves an area of denuded surface which has to be skin-grafted later and there is a certain amount of scarring. A graft from just below and posterior to the ear is the one of choice. Here there is no hair and the skin of this area has the same texture, thickness, and color as that of the nose. There is a negligible scar and it is in a location not readily noticed.

**Treatment of Chronic Laryngitis Simplex** by Dr. Louis H. Clerf, Philadelphia, Pa., was an interesting paper to those interested in surgery of chest conditions. Chronic laryngitis per se is rare. Ruling out the nose, throat, and nasopharynx, the next most likely focus is the chest. Bronchiectasis, tuberculosis, carcinoma, and benign tumors from their positions act as constant irritants to the larynx through coughing and expectoration. Provided the nose, throat, and pharynx are ruled out, every case of chronic laryngitis should have an x-ray of the chest; it is surprising how many chest conditions are picked up in this manner. Carcinomas at an early stage, after bronchoscopic biopsy, have been removed by the surgeon. Chronic laryngitis has led to the finding of severe bronchiectasis; and following lobectomy or pneumonectomy, the patient has gone back to a normal life. Whereas the bronchiectasis was the main factor, the laryngitis is only secondary.

**The Panel Discussion of Septic Sinus Thrombophlebitis** was led by Dr. L. W. Dean, St. Louis, Mo., Dr. George Tobey, Boston, Mass., Dr. A. C. Furstenburg, Ann Arbor, Mich., Dr. Samuel Kopetzky, New York, N. Y., Dr. H. I. Lillie, Rochester, Minn., Dr. Allen Hartmann, St. Louis, Mo., and Dr. John MacKenzie Brown, Los Angeles, Calif. This question has long been a topic of discussion throughout the various hospitals and medical centers of the country and an attempt has been made to arrive at an understanding between the different sections.

In the question on diagnosis there is no set rule, cases being reported without having had any external aural discharge so that like many other surgical conditions a careful history followed by a careful examination is our only lead. At the sudden onset of a lateral sinus involvement, there may be the characteristic chill followed by picket-fence temperature which fluctuates frequently within twenty-four hours. On the other hand the temperature may remain elevated with slight remissions, never reaching normal but varying little from time to time. Again, before the sinus is thrombosed, where there is a perisinus abscess, we may have remissions for twenty-four to forty-eight hours, followed by a slight rise due to absorption. Normal temperatures have been seen by all in the slow chronic type of infection where no involvement of the sinus is expected until the plate is uncovered. Blood counts help to rule out the lung and other fields; the higher the count the more likely one is to encounter other complications. The blood culture may be negative early, since the infection is fed through the small vessels and only later becomes positive as the sinus itself becomes involved. Where it has become involved by direct extension, however, the blood culture is positive early and the prognosis more guarded.

From an anatomic standpoint, few anomalies are met on the operating table; most are seen on cadavers or in the general routine postmortems. The sinus may end blindly near the lance, the petrosals taking its place; again it may be very small with hypertrophy of the emissary; on the other hand a very large sinus may be present at the expense of opposite side. One case was reported where it pierced the skull and appeared for a short time beneath the scalp before entering the skull again.

# REVIEW OF THE FORTY-SECOND ANNUAL SESSION OF THE AMERICAN ACADEMY OF OTOLARYNGOLOGY

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**T**HERE were many interesting and instructive papers presented at this meeting. Of the many papers there were some of interest to the surgeon, both in regard to surgery and in the cooperation the surgeon and otolaryngologist have established for the benefit of the patient.

**A Brief Summary of the Unsolved Problems in Otolaryngology by Dr. H. P. Mosher, Boston, Mass.** There are many questions unanswered, still, many interesting observations, which help to throw light upon some of these, but in the main there is much left to do. One problem has advanced and is partially overcome; namely, osteomyelitis of the frontal bone. Most of such cases result from an acute infection or from an exacerbation of a chronic frontal sinusitis. Much work has been done by Dr. Mosher and his staff advocating radical surgery with removal of the diseased bone including one-half to one inch of the surrounding healthy bone. With the established diagnosis and the knowledge that the infection has traveled one inch beyond the area of edema of the scalp, this radical procedure has met with good results and the mortality rate has greatly decreased. Not only should the anterior wall of the frontal be removed but the posterior wall as well, leaving the floor. A minimum of nasal surgery is done to the ethmoids at this time, only enough for established drainage through the anterior group of cells.

**A Review of Nine Cases of Malignant Disease of the Nasal Accessory Sinuses** was presented by Dr. Frank R. Spencer, Boulder, Colo., and Dr. W. C. Black, Denver, Colo. Nasal blockage and bleeding are the outstanding points in diagnosis, bleeding being the earliest sign. When nasal obstruction, swelling, pain, and foul discharge are complained of, the case has usually progressed beyond the stage of a hoped-for cure and only palliative surgery and deep therapy help to prolong the condition and relieve the symptoms, rather than removal or destruction of the growth. Of the malignancies epidermoid carcinoma is the most prevalent; and where it originates in the antrum or ethmoid the metastasis is by direct extension rather than by lymphatic or blood stream invasion. Here surgery has offered good results, but in the main, results are only partial; x-ray, too, has arrested the growth for a time. Where x-ray and surgery have been combined, the results have been favorable with the reports of many cures. The authors mention x-ray first because the vessels and lymphatics are sclerosed and sealed; there is less bleeding at the time of operation and less danger of metastasis through the lymphatics due to operative manipulation of the growth. Also, following operation, another period of x-ray treatment may be given within a reasonable time without danger to the patient and with much better effects than one massive postoperative dose.

**Plastic Repair of Deformities About the Lower Part of the Nose Resulting From Loss of Tissue** was presented by Dr. V. H. Kazanjian, Boston, Mass. He divides the amount of loss into four groups: first, the loss of only the skin of the nose; second, the loss of the tip; third, the loss of the tip and alae; and fourth, the loss of the mucous membrane of the nose. The causes are traumatic injury, carcinoma, angioma, tuberculosis, and syphilis. Before repair is attempted, all

# Book Reviews

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**Ross and Carless Manual of Surgery.** By Cecil P. G. Wakeley and John B. Hunter. Edited by William T. Coughlin. Ed. American (15). Cloth. Pp. 1,536, with 900 illustrations. Baltimore, Md., 1937, William Wood & Company. \$9.

The fifteenth American edition of this well-known English textbook, edited by W. T. Coughlin, purports to be a reliable textbook for students and general practitioners. Almost all subjects of practical surgical interest, except those of a gynecologic nature, are included within its 1,536 pages. The reviewer is somewhat disappointed, however, in failing to find many of the more recent refinements of surgical diagnosis and treatment with which the American surgeon is familiar. This failure to reflect adequately the recent progress in methods of diagnosis and treatment is the greatest criticism which can be made of the otherwise complete and admirable book. To cite specific examples: It is startling, to say the least, to find early incision recommended for cellulitis. The lack of emphasis accorded the roentgenologic examinations in the diagnosis of surgical conditions is typified by the absence of any mention of such examination in the section dealing with the diagnosis of intestinal obstruction. No mention is made of the injection treatment of inguinal hernia, nor of the conservative treatment of gastrointestinal stasis by suction applied to an inlying duodenal tube. The treatment of circulatory insufficiency by passive vascular exercises is omitted.

The book is written in a clear, concise style. The material is well organized and divided with many well-chosen subtitles. The illustrations are abundant and excellent.

Certain chapters are particularly good, especially those on "Injuries and Diseases of Arteries—Aneurism—Ligature of Arteries," "Injuries of Bones—Fractures," "Affections of the Brain and Its Membranes," "Diseases of the Breast," and "Amputations." The chapter entitled "The Use of Physical Agencies in Surgery" could be read with profit by anyone who has to deal with surgical conditions.

One wonders why the sections on gynecology have been omitted from the American edition when complete chapters dealing with surgical affections of the ear, nose, and throat have been included. An adequate index is appended.

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**Gastroscopy.** By Rudolph Schindler. Cloth. Pp. 343, with 96 illustrations in color. Chicago, 1937, University of Chicago Press. \$7.50.

This monograph is the first in the English language devoted to gastroscopy. The presentation of this subject by Dr. Schindler, an acknowledged authority on gastroscopy, should do much to popularize the use of this valuable addition to our armamentarium for gastroenterologic diagnosis. The author firmly establishes the fact that gastroscopy and roentgenologic methods when employed together are superior to any and all types of functional diagnosis, but one cannot safely be used with exclusion of the other.

The first portion of the book includes a comprehensive historical review of the development of gastroscopy and a study of the anatomy of the stomach from a gastroscopic view-point. Considerable space is devoted to details of technique which will prove invaluable to the beginner as well as to the more experienced gastroscopist.

As regards treatment (whether to tie or not), a question still remains, left to the judgment of the operator. If not thrombosed with a septicemia but definitely infected, then the jugular should be tied. Where the infection has extended along the jugular vein, that vein should be tied and severed. With an infected thrombus involving the sinus, the sinus is opened; the clot is removed until there is free bleeding from both ends and is then packed off and obliterated; the question of tying the jugular is left to the judgment of the operator. Over a series of cases there is little to choose from in regard to tying this type as shown by the case reports, and the option is again left with the operator.

Because a sinus is thrombosed does not mean one has to rush in to any prolonged and tedious operation, requiring a good bit of skill and fraught with grave consequences and complications. The sinus is to be opened if the thrombus is infected; the jugular may or may not be tied, but the first regard is the care and condition of the patient so that when the operation is undertaken one starts with as good a surgical risk as is possible under the circumstances.

The author presents beautifully the stages and planes of anesthesia, the signs of anesthesia, the depths of anesthesia required for control of reflexes associated with the various structures of the body, and the classification of surgical procedures which can be accomplished under the various planes of anesthesia.

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In the first chapter the author discusses the attitude and approach on the part of the nurse which are most likely to establish ideal relationships between her, her patient, and other persons with whom she comes in contact while doing surgical nursing.

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The chapter on chronic gastroduodenal ulcer presents the various pictures of the development of an ulcer, its complications, and the healing of an ulcer. The subject of gastritis is fully discussed. Inasmuch as this is the most common gastroscopic finding in the average clinical material, this means of study should throw considerable light on the controversial subject.

A chapter on tumors stresses the early diagnosis of carcinoma and its differentiation from benign ulcer and indicates that gastroscopic examination should bring to surgery earlier those cases in which determination of malignancy is difficult by other means. In the later cases this examination in conjunction with x-ray should permit a more accurate selection of cases for surgery, thus reducing the number of exploratory operations in the inoperable cases.

An interesting series of observations on the postoperative stomachs of both satisfactory and unsatisfactory end-result cases is presented. Studies of the motility, postoperative gastritis, recurrent and gastrojejunal ulcer are very instructive.

The book is well illustrated throughout and the numerous colored pictures in the appended atlas are especially commendable.

Because of the author's original work and extensive experience, this authoritative presentation of the endoscopic study of gastric pathology will be a valuable addition to any medical library. Its straight-forward style should evoke considerable discussion on the pathology of the stomach and stimulate interest in gastroscopic examinations.

**Inhalation Anesthesia—A Fundamental Guide.** By Arthur E. Guedel. Cloth. Pp. 172. New York, 1937, The Macmillan Company. \$2.50.

The foreword by Ralph M. Waters, professor of anesthesia, University of Wisconsin, outlines the author's rich background of experience and teaching out of which the book grew, and states: "As a result, the author has evolved a technique of teaching which has been found exceptionally fruitful in the hands of others as well as himself in the instruction of undergraduate and graduate medical students. The methods of Guedel have long been used by many of us. Personally, I am very happy at the prospect of having available the contents of this small book as an aid in my attempts to convey to medical students and young physicians the principles and practice of inhalation anesthesia."

The book differs considerably from those on anesthesia previously published. It is confined entirely to inhalation anesthesia. It does not deal too minutely with theory, but it presents all necessary facts of physics and physiology to make the mechanisms, the signs, and the favorable and unfavorable reactions in anesthesia understandable. The technique of open ether administration is given as a pattern in quite complete detail, together with the attendant physical mechanisms of vaporization, concentration, vapor pressures, pulmonary absorption, distribution, blood and tissue concentration and retention. One is told just how to begin the induction with open drop ether and just how to vary the administration and technique in response to various reactions. The description is well given and helpful to the student. The description of semiclosed and closed methods with both liquids and gases is dismissed with the simple statements that the principles are the same except that the carbon dioxide is disposed of by allowing partial escape or partial or complete absorption by soda-lime, and that liberated nitrogen dilutes the gases and should be dispensed with by occasionally emptying the bag. However, the author is able to give good ether instruction without lessening the emphasis on principles and one wishes he had given the same concerning the closed methods. If it is helpful and desirable to give one, it should be helpful and desirable to give the other.

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VOLUME 2

JULY—DECEMBER, 1937

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ST. LOUIS  
THE C. V. MOSBY COMPANY

1937

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Printed in U. S. A.

*Press of*  
*The C. V. Mosby Company*  
*St. Louis, Mo.*

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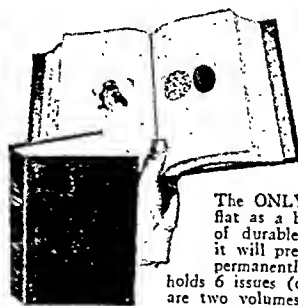
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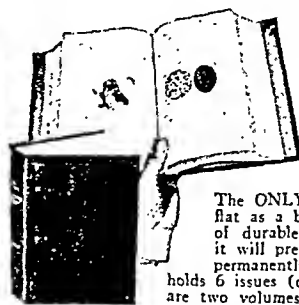
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Published by THE C. V. MOSBY COMPANY, 3525 Pine Blvd., St. Louis, U.S.A.

Great Britain Agents: Henry Kimpton, Ltd., 263 High Holborn, London, W.C.1.  
Entered at the Post Office at St. Louis, Mo., as Second-Class Matter.

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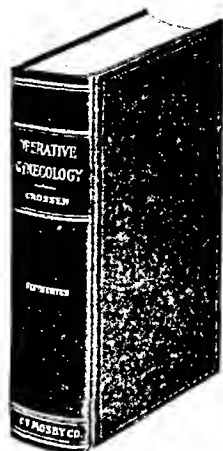
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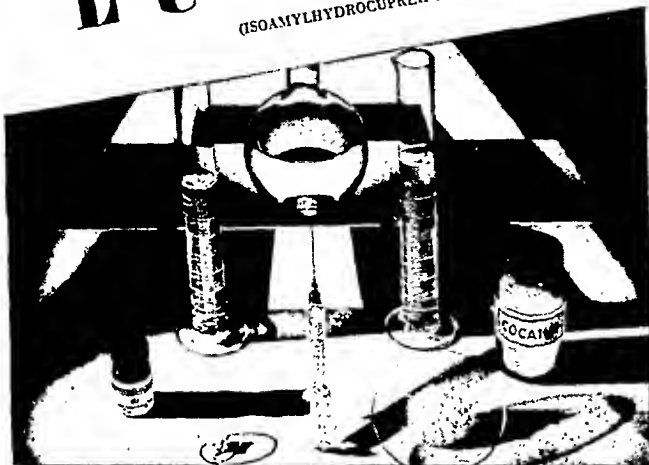
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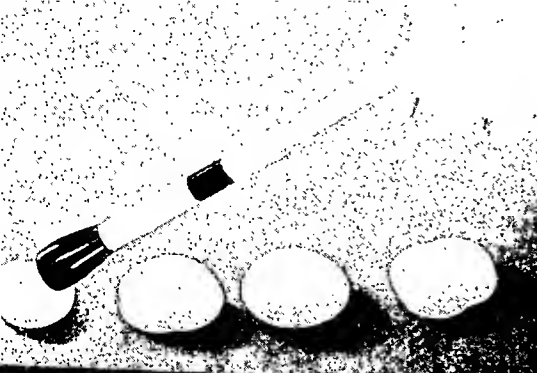
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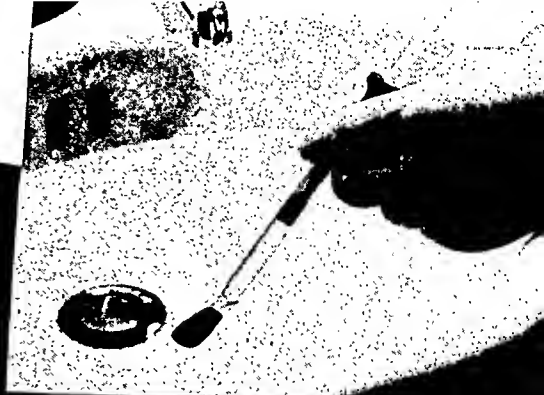
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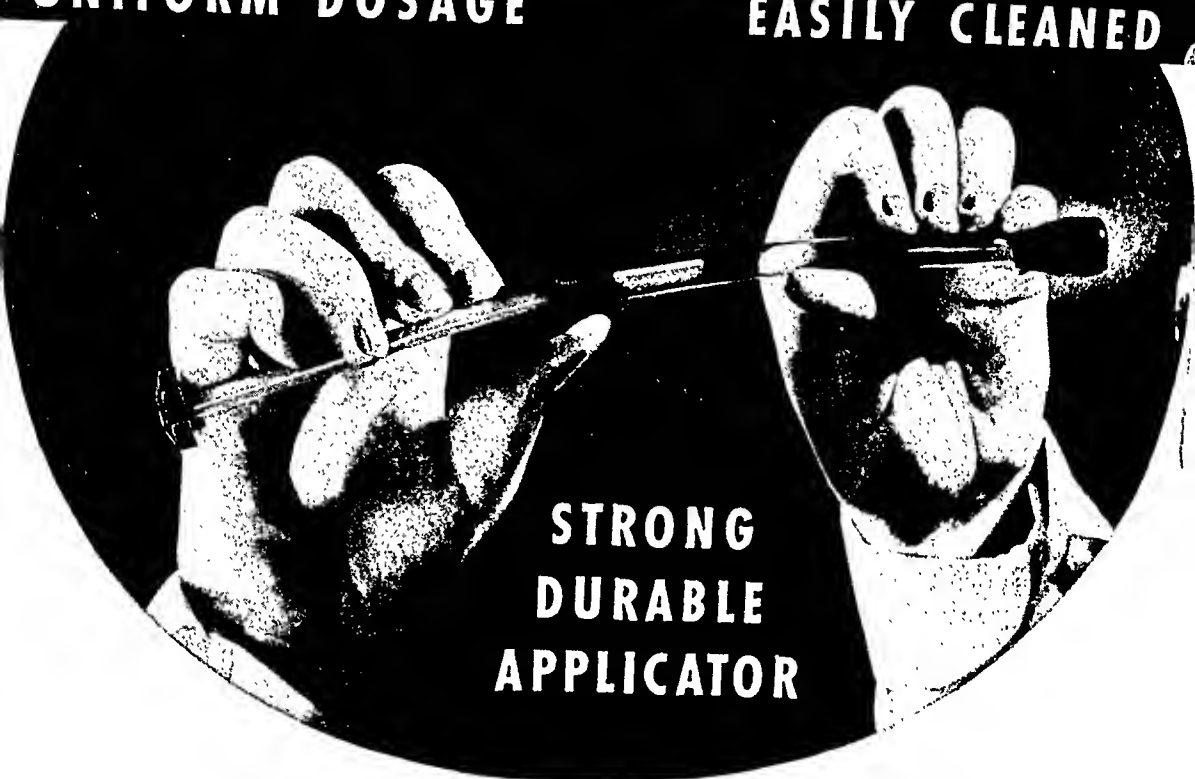
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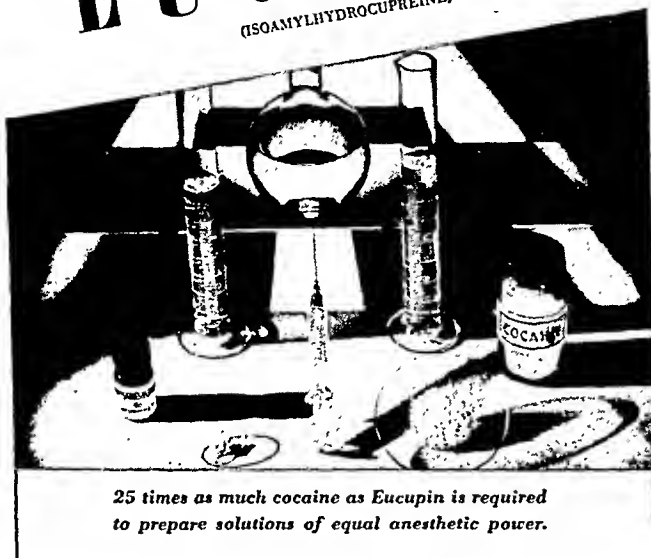
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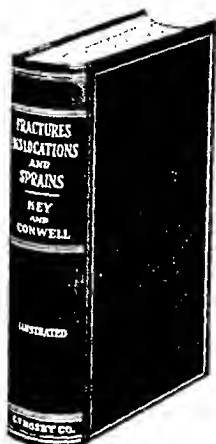
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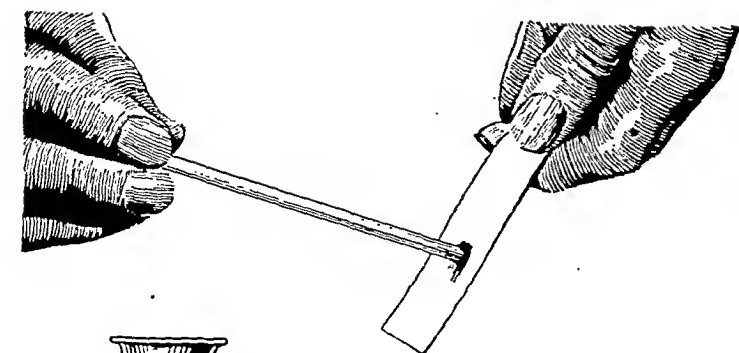
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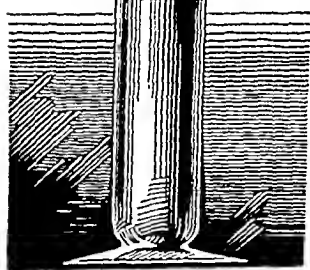
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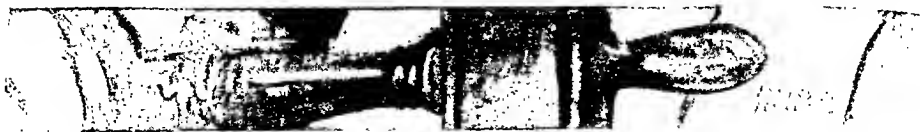
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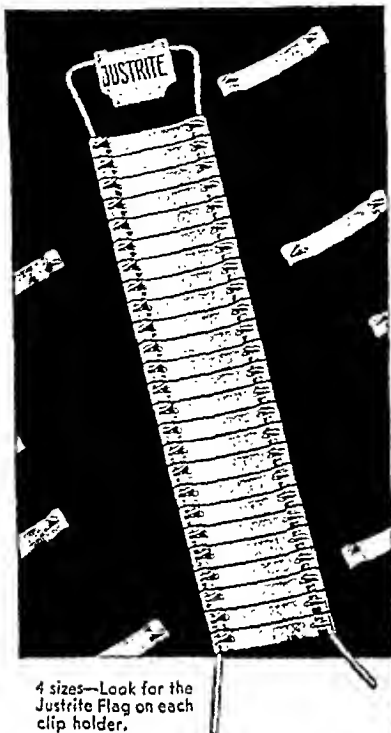


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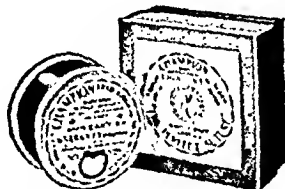


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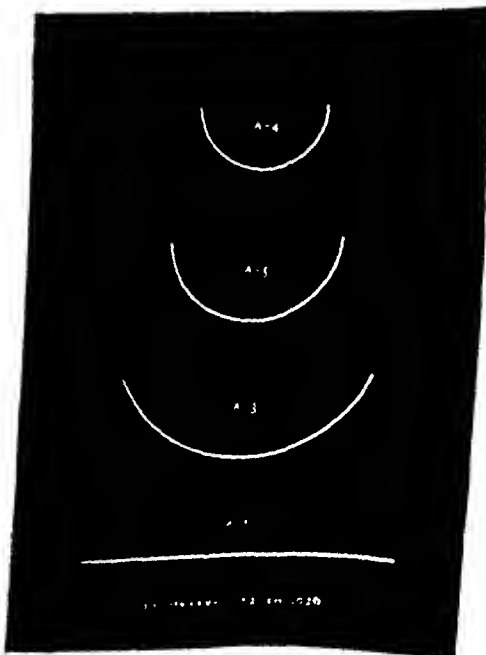
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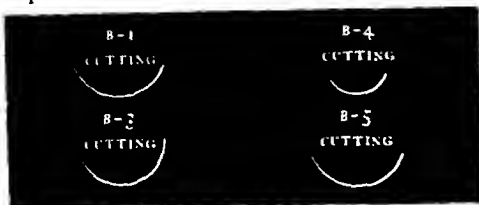
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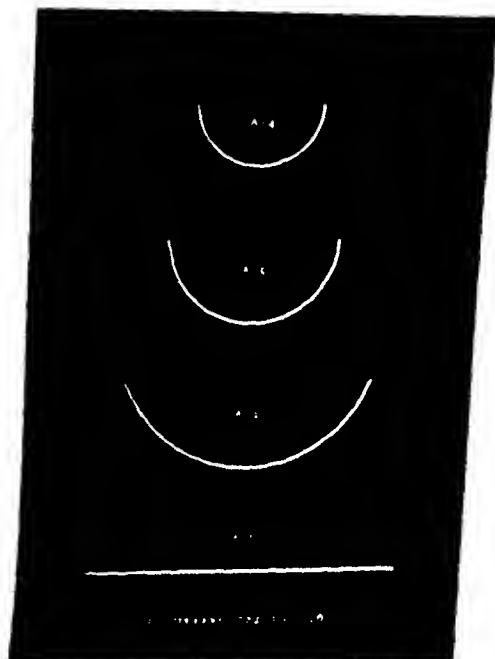
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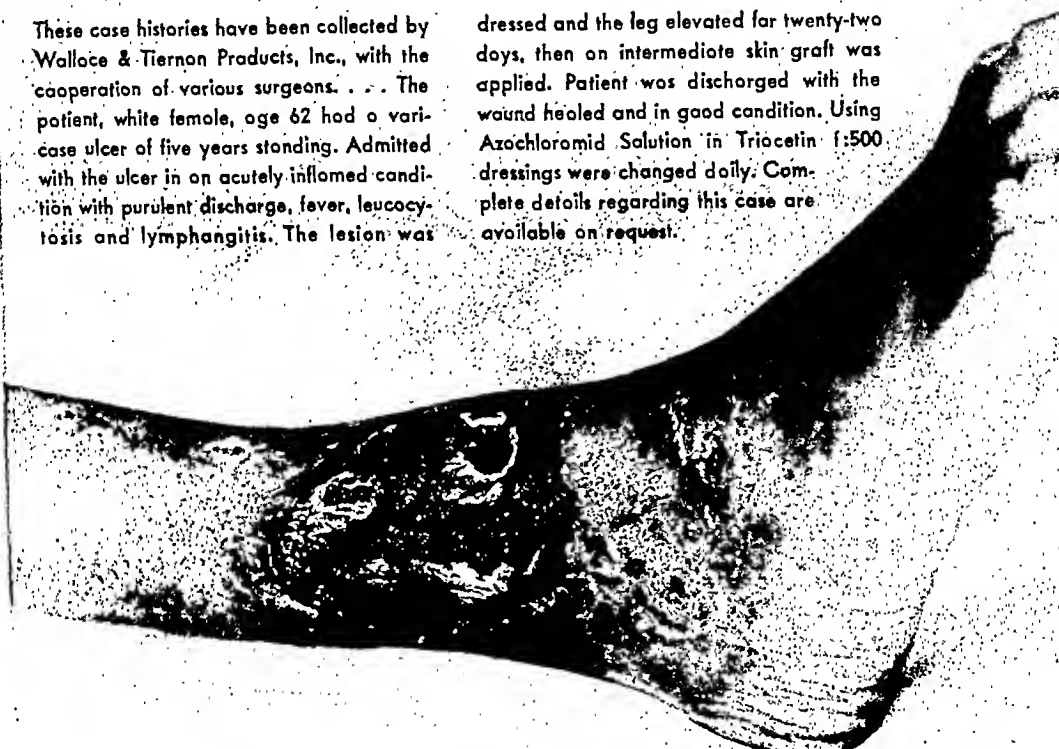
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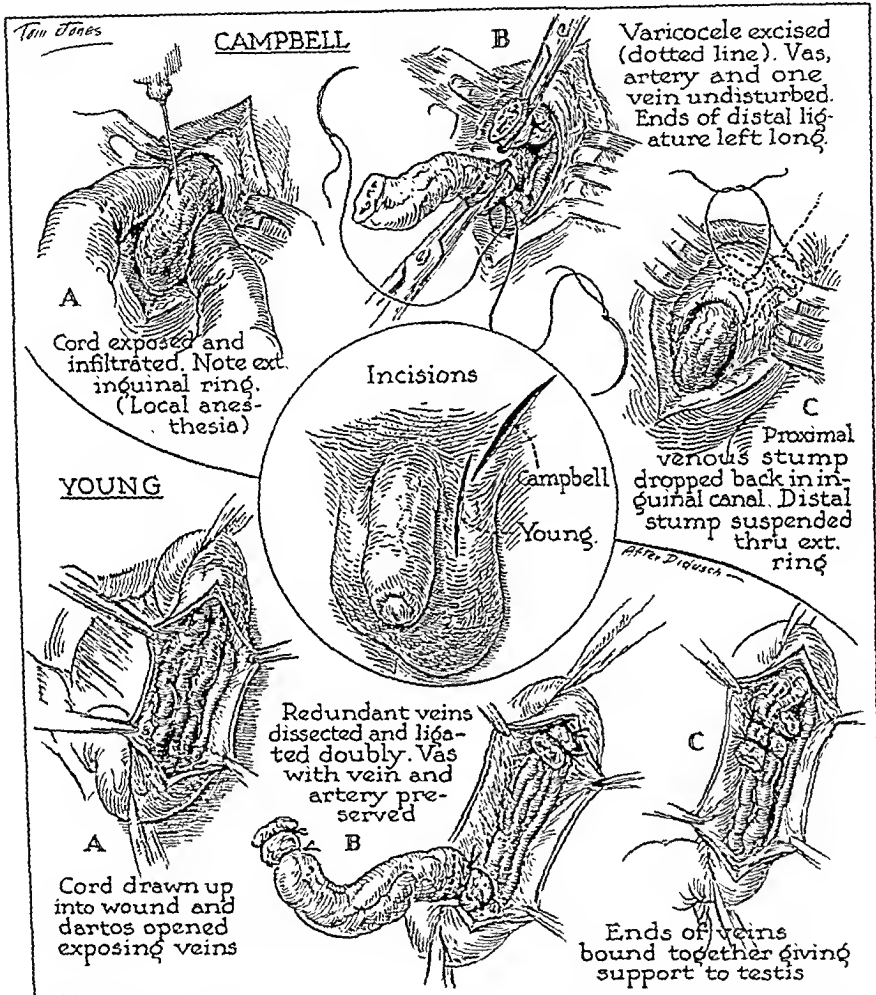
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# SURGERY

VOL. 2

NOVEMBER, 1937

No. 5

## Original Communications

### Symposium on Peptic Ulcer

#### THE PHYSIOLOGY OF PEPTIC ULCER

MICHAEL DEBAKEY, M.D., NEW ORLEANS, LA.

*(From the Department of Surgery, Tulane University School of Medicine)*

THE rapid strides that have marked surgical progress during the past few decades have been due in the main to the continuous endeavor to correlate experimental physiologic alterations with aberrant clinical manifestations and to the more recently acquired clinical attitude of developing a therapeutic attack through a thorough comprehension of the disordered physiology. Rationale, i.e., the logical basis of a procedure, is the essence of present-day surgical therapy. Thus, the importance of physiology becomes obvious because a rational therapeutics can be developed only through a complete understanding and correlation of the fundamental physiologic principles and their derangement in disease.

The subject of peptic ulceration is indeed an excellent example of this form of progress and the important significance of a comprehension of the underlying physiologic alterations. Any attempt to discuss intelligently this paramount condition without an exposition of the physiologic mechanisms involved in its development would be nugatory.

The voluminous clinical, statistical, and experimental investigations that are perennially contributed on this subject attest to its bewildering pathogenesis. Because of the prominence of the local ulcerative lesion and the specialized interests of the various workers, most studies have been unwittingly focused on the ulceration per se, and, instead of clarifying the problem, they have merely added to the existing maze of confusion. Whereas this has given rise to multifarious hypotheses and to diversity of opinion which clearly reveal the perplexing problems of its causation and make it safe to assume that no one factor can be held

Received for publication, September 23, 1937.

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responsible for ulcers in general, nevertheless certain factors have emerged as playing important rôles in the etiology and pathogenesis of the disease. It is our purpose here to analyze and discuss, from the physiologic standpoint, these factors whose importance in the development and maintenance of peptic ulceration have been indicated through experimental and clinical investigations. These factors may be classified under the following captions: (1) constitutional, (2) chemical, (3) tissue susceptibility, (4) mechanical or traumatic, and (5) infection.

*The Constitutional Factor.*—The importance and existence of an inherent factor predisposing to the development of ulcer in certain individuals can no longer be denied, but it is extremely difficult to define or state exactly what constitutes this factor. Whereas it has been possible to investigate certain phases of this problem in the experimental laboratory, most of the evidence has come from clinical observations and investigations. Among the first to direct attention to this innate characteristic were Draper and others.<sup>1</sup> Their studies revealed that the ulcer-bearing patient has certain characteristic anthropometric relations as well as certain psychologic factors which are measurable components of the "ulcer constitution." Stenbuck<sup>2</sup> made similar observations and expressed the belief that these individuals have characteristic facies, which are usually thin and drawn with high malar prominences, are poorly nourished and energetic in demeanor, and present an anxious expression. Hurst<sup>3</sup> believes that the essential predisposing factor in the production of duodenal ulcer is the presence in an individual of hypersthenic gastric diathesis, which manifests itself in hypertonus and hyperchlorhydria. He is of the opinion that its occurrence in several members of a family suggests its probable hereditary character. This familial tendency has also been stressed by Huddy<sup>4</sup> and McVicar<sup>5</sup> as well as by others. The recent studies of Meyer and others<sup>6</sup> are of interest in this regard. An analysis of the gastric secretion in a large group of healthy members of "ulcer families" revealed an abnormal response to the Ewald meal and a high acidity of the resting stomach. They interpreted the results obtained as an "expression of an abnormal gastric mechanism, so far unknown, which may produce both abnormal secretion and ulcer." Wilkie<sup>7</sup> states "there is a type of individual peculiarly prone to ulcer and that heredity plays a part."

Other investigators have attempted to define this ingrained characteristic in a more specific manner. With a capillary microscope Müller and Heimberger<sup>8</sup> examined fresh specimens immediately following partial gastrectomy and found spasm and atony of the arterioles, capillaries, and venules of the gastric mucous membrane. They refer to this as a "vasoneurotic diathesis" which they believe is a congenital or acquired "disharmony" in the structure and function of these small blood vessels. Many observers have stressed some derangement of the nervous system as the most significant single factor in the causation of

peptic ulceration. Supposedly there exists a "disharmony" between the vagi and their anatagonists, the sympathetics, which leads to disturbances in secretory and motor functions. The constant, irritating nervous stimuli eventually lead to localized spasmophilia of the duodenal or gastric musculature, which in turn effects areas of mucosal or submucosal ischemia. The final erosion of the mucosa is due to the consequent diminished resistance in these localized areas, and the prolongation of this nervous irritability with the resulting hyperacidity accounts for the production of chronicity. According to this hypothesis all ulcers fall into two classes; viz., vagotonic with abnormally increased vagus tone or sympathicotonic with abnormally increased sympathetic tone. Experimental investigations along this line have followed three methods of approach: (1) severance<sup>9-12</sup> or stimulation<sup>11, 13, 14</sup> of the vagi; (2) irritation or extirpation of the sympathetics and celiac plexus<sup>15-19</sup>; and (3) irritation or stimulation of the central nervous system.<sup>20, 22, 31</sup> Physiologists are now agreed there are at least three phases in normal stimulation of gastric secretion. The initial or cephalic phase is dependent upon psychic stimuli mediated by the vagi. Some observers<sup>23-26</sup> have suggested that hyperactivity of the vagi may produce an increase in the rate of secretion of the gastric acids which in turn is conducive to ulceration. In a recent publication Ferguson<sup>27</sup> reviewed this phase of the subject and concluded that; whereas, vagotomy is more likely to produce hemorrhagic lesions and acute erosions than true chronic ulcers, splanchicotomy and adrenalectomy are probably even more effective in producing such lesions. The results obtained in his own experiments on the effects of vagotomy on gastric functions of monkeys demonstrate that the "gastric and intestinal phases of acid and chloride secretion are well able to continue in spite of the operative severance of the vagus nerves." Crile<sup>28-30</sup> has been one of the leading advocates of sympathico-adrenal hyper-irritability in ulcer development. Experimental investigations on this relationship have met with varying degrees of success.<sup>31-35</sup> Wolff and Thomas<sup>36</sup> studied a group of patients with gastric neuroses and ulcer and found evidence of autonomic imbalance. These authors believe that irritative impulses, either central or peripheral, may be conveyed by means of the vagus nerve and sometimes, although rarely, by the thoracolumbar branches through the gastric and duodenal systems. As a result of his observations on the simultaneous occurrence of cerebral lesions and peptic ulcer, Cushing<sup>37</sup> has suggested that irritative disturbances in the vagal centers of the brain stem, resulting from worry, anxiety, and heavy responsibility, may produce chronic hyperacidity, often effecting ulceration. Stimulated by these clinical observations numerous investigators have attempted to adduce evidence indicating a causal relationship between intracranial involvement (hypothalamus,<sup>38-42</sup> hypophysis,<sup>43</sup> cerebral cortex<sup>44</sup>) and certain gastrointestinal disturbances. It is very difficult to draw positive conclusions from the results of these investigations, but



in general they seem to assign a definite significance to neural derangements in the genesis of ulcer. The importance of psychic trauma in the development of peptic ulcer has been emphasized by Rivers.<sup>45</sup> Among 200 specialists in medicine, he<sup>45</sup> found an almost 20 per cent incidence of peptic ulcer and an additional 20 per cent who admitted taking alkalis at intervals. He stated that these findings are of more significance in comparing the results in a similar study among 200 negroes, in none of whom ulcer was encountered. Steigmann,<sup>46</sup> however, stresses the psychogenic factor even in the negro, because he found a 12.7 per cent ulcer incidence, and states that these northern negroes are vastly different from the indifferent types of Texas negroes. He is of the opinion that "environmentally conditioned psychic factors play an equally important rôle in the genesis of peptic ulcer in white and negro patients." Robinson<sup>47</sup> believes that emotional conflicts in an individual with ulcer diathesis are alone essential for the production of chronic gastroduodenal ulcer. He<sup>48</sup> advances the view that "these individuals with their fears and anxieties develop an imbalance of the vegetative nervous system." On the assumption that the "anxiety complex" may cause ulcer by producing a condition of sustained gastric hypersecretion and hypermotility, Orndorff, Bergh, and Ivy<sup>49</sup> studied this factor experimentally by inducing this state pharmacologically. Although acute lesions were common, no chronic ulcers developed.

#### CHEMICAL FACTORS

A disturbance in the chemical and physiological relationship of the acid gastric juices on one side and the alkaline duodenal secretions on the other in the development and maintenance of peptic ulceration has long been suspected. Whereas the accumulated clinical and experimental evidences have established its indubitable significance, nevertheless its exact nature is still imperfectly understood. The strictly limited localization of the occurrence of ulcer with striking uniformity in only those areas which are habitually bathed in acid chyme and in other parts of the intestinal tract only under exceptional circumstances which permit exposure to the gastric secretion has indicated the culpability of the acid gastric juice. Investigators throughout the world have been stimulated to produce experimental evidence to substantiate the possibility of an insufficient neutralization; i.e., some abnormal inability of the alkaline duodenal juices to neutralize the normal or probably hyperacid gastric secretion or to demonstrate some factor which might be totally absent, abnormally increased, or unusually diminished. It will, of course, be impossible to attempt here a detailed review of the enormous clinical and experimental data that has accumulated in support of this factor. It will be necessary to confine this discussion to a brief outline of the more pertinent clinical and experimental facts.

Considerable importance has been attached to the frequent occurrence of hyperacidity in patients with peptic ulcer. Studies of large groups of gastroduodenal ulcer cases have demonstrated that there occurs a normal acidity in approximately one-third of the cases and a hyperacidity in almost one-half.<sup>50-55</sup> Although it is generally believed that there is no diagnostic acidity curve in gastric ulcer, hyperchlorhydria with hypersecretion is thought by many to be almost pathognomonic of active duodenal ulcer.<sup>56-59</sup> The interesting studies on the interdigestive phase of gastric secretion are particularly enlightening in this respect. During such fasting periods the acid gastric juice, undiluted and unneutralized, may be especially harmful to the mucosa. Obviously, the gastric secretory activity during sleep at night should be the most significant because this is the longest fasting period. Such investigations clearly reveal that normal subjects have a characteristic nocturnal secretory rest in contradistinction to ulcer patients whose gastric secretion is unusually active and contains uniformly high acid values.<sup>60-63</sup> The effect of experimentally produced hyperacidity by the feeding of dilute hydrochloric and other acids has been studied by many investigators.<sup>30, 64-72</sup> Whereas such an artificial hyperacidity may produce lesions ranging from simple erosions to actual ulceration, the conclusions reached by most of these observers was that it is of no significance except in considerably higher percentages than that found in the human stomach even in the presence of ulcer.

Because of its stimulating effect on gastric glands,<sup>73-75</sup> histamine has been extensively employed in studies of ulcers experimentally produced in various animals, such as the rat,<sup>76-79</sup> the cat,<sup>80, 81</sup> the rabbit,<sup>82</sup> and the dog.<sup>72, 82, 83</sup> The results obtained by most of these observers indicate that histamine by its stimulative action on gastric juice is capable of producing changes in the mucosa varying from simple erosion to acute and chronic ulcers. In an attempt to evaluate the significance of increased gastric acidity obtained by feeding hydrochloric acid and by stimulation with histamine, Ochsner, Gage, and Hosoi<sup>83</sup> found that erosions or ulcers developed in 27 per cent of the animals studied.

Relatively recently it has been adequately demonstrated that by the oral administration of cinchophen, it is possible in the dog to produce ulcers consistently, having all the characteristics of those observed in man.<sup>84-88</sup> The importance of the acidity factor in the development of such ulcers has been clearly demonstrated by Stalker, Bollman, and Mann.<sup>86-88</sup> In an interesting group of rigidly controlled experiments they showed that the presence of free hydrochloric acid was essential for the development of peptic ulcers produced by cinchophen.

In order to study the influence of gastric acidity better, numerous experiments have been devised to evaluate the significance of the counter-acting neutralizing effects of the alkaline duodenal secretions. The

diversified and numerous procedures devised for this method of approach practically all have a similar underlying principle and their purpose in the majority of instances has been to determine the relative protective values of the alkaline juices alone and in combination with each other.

Bickel<sup>89</sup> was one of the earliest to recognize the importance of the alkaline duodenal secretions in preventing the formation of ulcer. In 1909 he performed duodenectomy in two dogs after closure of the pylorus, reestablished continuity of the gastrointestinal tract by gastroenterostomy, and sutured the bile and pancreatic ducts to the skin of the abdomen. One month later one dog died of perforation with resulting peritonitis of one of several jejunal ulcers just distal to the stoma. Five years later Langenskiöld<sup>67</sup> devised an experimental operation on the dog which eventually led to the more consistent ulcer-producing procedure of Mann and Williamson.<sup>90</sup> After severing the duodenum just proximal to the opening of the bile duct and closing the distal end, he severed the jejunum several centimeters distal to the duodenum and anastomosed the distal end to the proximal end of the duodenum and joined the proximal end of the jejunum to a loop of jejunum further caudad. Thus bile and pancreatic juices were shunted to the lower part of the small intestine. The animal was sacrificed a month later, and an ulcer was found in the short segment of the duodenum between the stomach and the jejunum. In 1923 Mann and Williamson<sup>90</sup> slightly modified Langenskiöld's operation by severing the duodenum at the pylorus and at its junction with the jejunum, closing its oral end, and anastomosing its distal end to the terminal portion of the ileum, and then anastomosing the proximal end of the jejunum to the pylorus. This "surgical duodenal drainage" procedure shunted the entire alkaline duodenal secretions away from the jejunum and into the lower ileum and resulted in the consistent development of typical chronic ulcers in the jejunum just distal to the gastrojejunal stoma. These results have been corroborated by many other investigators.<sup>91-94</sup> It has been irrefutably established that deviation of all the alkaline duodenal juices will inevitably result in the formation of such ulcers.

These procedures effect a persistent state of high gastric acidity, which might account for the production of ulcer. Because Boldyreff<sup>95</sup> maintained that the acidity of the gastric juice is regulated by the regurgitation of the duodenal alkali into the stomach, experiments have been devised to determine whether or not a reflux of the entire duodenal contents into the stomach prevents or heals ulcers. Chlunsky,<sup>96</sup> Schmilinsky,<sup>97</sup> and Keppich<sup>98</sup> obtained no ulcer after these experiments; on the other hand, McCann<sup>99</sup> obtained jejunal ulcers in 80 per cent of twenty-six dogs. Graves<sup>100</sup> slightly modified the McCann procedure so that instead of deviating duodenal secretions into the fundus of the stomach it was deviated into the prepyloric region, and he obtained no ulcers in his group of experiments. Weiss, Graves, and Gurriaran<sup>101</sup>

confirmed these findings. These experiments emphasize the importance of gastric acidity in the genesis of ulcer, especially in the absence of the neutralizing effect of the alkaline duodenal secretions.

Because of the obvious protective value of the alkaline duodenal juices in preventing the formation of ulcer, numerous experiments have been performed to determine which of these secretions, if any, that is, the succus entericus, the pancreatic, or the biliary juices, plays the feature rôle. Although these procedures are diversified in nature, the underlying principle of excluding one or more of these juices either separately or in combination has been the same. The effect of the combined deviation of bile and pancreatic juices, thus permitting the protective influence of the succus entericus to remain, has been studied with varying and contradictory results.<sup>90, 102-104</sup> By eliminating only the duodenal secretion and thus permitting the bile and pancreatic juices to remain, the protective influence of the succus entericus has been indirectly determined.<sup>90, 93, 105, 106</sup> Graves<sup>100</sup> performed duodenectomy in three stages and came to the conclusion reached by most of the other observers that in the experimental animal the duodenum is apparently not essential to life and its secretion alone is not altogether sufficient protection against the formation of ulcer. On the other hand, Mann and Bollmann and their coworkers,<sup>98, 107, 108</sup> as a result of their investigations, contend that the duodenal mucosa and secretions are the most important in preventing ulcer formation.

The protective influence of pancreatic juice has been determined indirectly by its elimination either by total pancreatectomy, by ligation, by transplantation of the pancreatic duct, or by the production of a fistula in the pancreatic duct.<sup>100, 103, 109-116</sup> The results obtained by most of these observers indicate that pancreatic juice does not have an important protective influence in the production of ulcer. In contrast to this, however, Elman and Hartmann,<sup>117</sup> Matthews and Dragstedt,<sup>118</sup> and Hoerner<sup>119, 120</sup> found evidence that pancreatic juice has a definitely protective influence against ulcer formation. Hoerner<sup>121-123</sup> further emphasized the importance of the acid neutralizing effect of the pancreatic secretion by demonstrating its quantitative buffering capacity and the effect of its exclusion on the pH of the gastric duodenal and jejunal contents.

The influence and the effect of the biliary secretions have been studied by methods similar to those used in the study of the pancreatic secretions. Kapsinow<sup>124</sup> deviated bile in dogs to the pelvis of the kidney and obtained a relatively high incidence of ulcer formation. Others<sup>93, 100, 103, 116, 125, 126</sup> deviated the bile into the lower portion of the ileum and obtained ulcers in a relatively high incidence of the animals. Rous and McMaster<sup>127</sup> studied the effect of the exclusion of bile by a special sterile fistula method and noted no ulcer formation. On the

other hand, Berg, Johnson, and Jobling,<sup>114, 128</sup> using a similar method, obtained ulcers in a relatively high incidence. Blanck<sup>129</sup> not only showed that such complete external drainage of bile resulted in ulcer formation, but also that the incorporation of fresh bile in the feedings of these dogs could prevent the development of these ulcers. However, Mann and Bollmann<sup>68, 107</sup> minimize the protective influence of bile. Working in their laboratory, McRoberts<sup>130</sup> attempted to support their contention by demonstrating that the pH of the duodenal contents is not significantly altered following the loss of bile. Ochsner, Gage, and Hosoi<sup>83</sup> have rather convincingly demonstrated the protective influence of bile. After performing a gastric pouch of the Heidenhain type from the greater curvature and of the Paylov type from the lesser curvature, they<sup>83</sup> anastomosed the proximal portion of the jejunum to the pouch. Ulcers occurred in 100 per cent of the animals in which the former procedure was done and in 71 per cent in which the latter procedure was done, or an average of 85 per cent. In another series in which the procedure was similar to the foregoing, but with the addition of anastomosis of the fundus of the gallbladder to the pouch, the incidence of ulcer was reduced from 100 to 28 per cent in the Heidenhain pouch dogs and from 71 to 50 per cent of the animals with a Pavlov pouch, or from an average of 85 per cent in the first series in which there was no bile present to 39 per cent in the latter group in which bile was present.

Because of the difficulties in drawing conclusions from the confusing and contradictory experimental results obtained by different observers in attempting to evaluate the relative protective influence of each of the alkaline duodenal juices, I<sup>131</sup> performed a series of rigidly controlled experiments. A total of sixty dogs was used and divided into four groups. In the first group the pylorus was severed and the gastric and duodenal ends were closed. Continuity was reestablished by anterior gastro-jejunostomy. In the remaining three groups a similar procedure was performed, but with the addition of ligation and division of the accessory pancreatic duct and transplantation of the main pancreatic duct into the terminal portion of the ileum in Group II, the transplantation of the common bile duct into the terminal portion of the ileum in Group III, and the transplantation of both the bile and pancreatic ducts into the terminal portion of the ileum in Group IV. In this way all of the animals were subjected to the same extrinsic factors except one, the deviation of pancreatic juice in the second group, the deviation of bile in the third, and the deviation of both bile and pancreatic juice in the last group. In the first group in which none of the alkaline duodenal juices were deviated, 50 per cent of the animals developed ulcer; in the second group in which pancreatic secretion was deviated, 70 per cent of the animals developed ulcer; in the third group in which bile was deviated, 90 per cent of the animals developed ulcer, and in the fourth

group in which both pancreatic juice and bile were deviated, all of the animals developed ulcer. Based upon these experimental results, bile seems to have the most significant and effective influence in preventing the formation of jejunal ulcer. Of the duodenal secretions, the succus entericus apparently is the least important, and the pancreatic juice seems to be midway between the two in this respect.

Another link in the chain of evidence against the etiologic significance of acid peptic activity of the gastric secretion is the consistent relationship of peptic ulceration and acquired and congenital heterotopia. Meckel<sup>132</sup> first described the diverticulum which bears his name in 1815, and now the clinical picture of ulceration and perforation resulting from the adjacent dystopic gastric mucosa producing its acid peptic secretion present in Meckel's diverticulum is definitely established.<sup>133-136</sup> Mondor and Lamy<sup>137</sup> recently reported nearly 100 cases of ulcers of Meckel's diverticulum. Artificially produced Meckel's diverticula in the experimental animal have also resulted in a high incidence of peptic ulcer.<sup>118, 138-140</sup>

Numerous observers have noted that condiments, alcohol, and tobacco are aggravating to patients with peptic ulcer.<sup>141-144</sup> The deleterious influence of these substances is probably twofold; viz., the direct irritative effect on the gastric and duodenal mucosa resulting in gastritis and duodenitis, and the indirect effect on gastric secretion resulting in hyperacidity. Alcohol is such a powerful stimulant of gastric secretion that it is frequently used as a test meal.<sup>145, 146</sup> That tobacco smoking produces hyperacidity and is, therefore, detrimental to ulcer patients has been demonstrated by many investigators.<sup>147-150</sup>

From the foregoing brief review of the clinical and experimental investigations, it can readily be observed that the acidity factor plays an important rôle in the genesis of peptic ulceration. It can no longer be doubted that pure, undiluted gastric juice can produce ulcer. Obviously, many of the experimental states resulting in ulcer by the establishment of unphysiologic conditions do not exist in the human being. However, they demonstrate convincingly the significance of acid peptic secretions. Whether in the human this acidity factor becomes relatively more important because of faulty or improper neutralization or because of overactivity due to some stimulative effect cannot be definitely stated, but its real significance can no longer be denied.

*Tissue Susceptibility.*—The significance of tissue susceptibility as a predisposing factor in the genesis of ulcer has resulted from experimental and clinical investigations which reveal that certain portions of the gastrointestinal tract, namely, the lesser curvature of the stomach (ungenstrasse), the duodenal cap, the jejunum, and other portions of the intestinal tract subjected to acid gastric secretions, seem to have an inherent vulnerability to peptic ulceration. Obviously, this factor

is closely related to the acidity factor, because ulceration rarely occurs in these areas unless they come in contact with acid gastric chyme. However, their strictly limited localization with striking uniformity cannot be solely explained by the acid peptic activity of the gastric secretion. The bulk of evidence indicates that they possess an intrinsic quality of susceptibility; or to state it differently, there would appear to be an inherent lack of the ability to resist the digestive eroding effect of the acid gastric juice.

It has long been known that gastric ulcers frequently occur along the lesser curvature and that ulcers rarely develop along the greater curvature in spite of the fact that the greatest acid secreting area in the stomach lies in the fundus. Morton<sup>151</sup> observed that after "surgical duodenal drainage" ulcers along the greater curvature healed; whereas, those on the lesser curvature became chronic. Gage, Ochsner, and Hosoi<sup>152</sup> have very convincingly demonstrated this greater sensitivity of the mucosa along the lesser curvature to peptic ulceration. In one group of experiments the greater and lesser curvatures of the stomach were respectively extirpated. Whereas the incidence of ulceration was 63.8 per cent in those cases in which the lesser curvature remained after extirpation of the greater curvature, no ulcers developed in the group in which the greater curvature remained after removal of the lesser curvature. These experiments more clearly demonstrated the importance of tissue susceptibility when it is recalled that ulceration occurred in a relatively high incidence in that group of experiments in which the acid-bearing area of the stomach was removed, that is, the greater curvature. That a definite gradient in susceptibility to ulcer occurs with the aboral distance from the pylorus has been shown by many investigators. McCann<sup>99</sup> and Ivy and Fauley<sup>153</sup> so modified the Mann-Williamson procedure that a small segment of duodenum remained interposed between the stomach and jejunum, and they observed that in these animals the ulcers always formed in the jejunum, indicating that it was more susceptible to injury than is the duodenum. Mann and Bollmann,<sup>68</sup> Harper,<sup>140</sup> Matthews and Dragstedt,<sup>118, 154</sup> and McMaster<sup>155</sup> have definitely corroborated the fact that there is a commensurable susceptibility of the intestinal tract to acid gastric peptic activity as the distance from the pylorus is aborally increased. Matthes<sup>156</sup> long ago showed that hydrochloric acid would more easily injure the ileum than the jejunum and the duodenum. The frequent occurrence of ulceration in the intestinal mucosa immediately adjacent to existing gastric mucosa in a Meckel's diverticulum further supports this premise.<sup>155, 156</sup> This condition has been experimentally duplicated by making small Pavlov pouches of gastric wall which were transplanted into the ileum with the resultant development of ulcers.<sup>118, 154</sup> Gage, Ochsner, and Hosoi<sup>152</sup> also noticed similar ulceration when the jejunum received this acid gastric juice. This is further supported by the clinical observations of the de-

velopment of jejunal ulcers following gastrojejunostomy. Although the recorded incidence of jejunal ulceration following gastrojejunostomy in human beings reveals a marked variance of from 1 to 2 per cent to as high as 52 per cent,<sup>157-168</sup> it occurs with sufficient frequency to bear a real significance.<sup>169</sup> As a result of his own statistical survey which reveals that of thirty-one gastroenterostomies performed for benign lesions, 48.3 per cent developed jejunal ulcers, and a study of the literature, Newburger<sup>170</sup> emphatically condemns the procedure in the treatment of gastroduodenal ulcer. The increased susceptibility of the jejunal mucosa to ulceration has been further confirmed by other experiments performed in the Tulane Surgical Laboratory. In a series of twenty dogs in which pyloric occlusion and gastrojejunostomy were performed, jejunal ulcers developed in 50 per cent.<sup>171</sup> This is admittedly a high incidence, but why should ulcers develop at all after this procedure? The gastrointestinal physiology does not seem to be altered to such a commensurable degree; there is no deviation of alkaline juices; and the gastrointestinal acidity should not be increased. It would appear that the best possible explanation is that the jejunal mucosa is functionally unable to receive acid gastric chyme, and this factor is relatively more pronounced after this procedure as the pyloric occlusion does not permit a regurgitation of the alkaline duodenal juices into the stomach to help neutralize the gastric acidity.

*Mechanical or Traumatic Factor.*—Aschoff<sup>172</sup> was one of the first to stress the importance of the mechanical factor. His conception was based upon a comprehension of the function of the so-called "magenstrasse" or gastric pathway, which is formed by the characteristic arrangement of the folds of the gastric mucosa along the lesser curvature and is assumedly the route by which gastric chyme is propelled from the pylorus into the duodenum. Mann<sup>173</sup> contends that there are two important factors in the causation and prevention of healing of ulcers produced by their "surgical duodenal procedure"; namely, a chemical and a mechanical factor. He emphasizes the fact that an ulcer develops at the site where the mucosa is subjected to the greatest force of impingement of the gastric chyme as it is propelled from the stomach in a nozzle-like manner. To emphasize this propulsive action further Mann<sup>173</sup> performed the "surgical duodenal drainage" operation and then produced a typical hourglass stomach in the prepyloric region so that the stomach was divided into pouches, communicating at the lesser curvature through a small opening. In this manner the propulsive power of the stomach was considerably lessened, and these animals were remarkably resistant to the development of ulcer. McCann<sup>174</sup> further stressed the importance of this mechanical factor by the demonstration in one ulcer specimen of fifty or more hairs of the dog embedded in the sloping wall of the distal half of an ulcer. He surmised that the gastric chyme was thrown against this segment with sufficient force to embed the hairs



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infection, usually apparently innocuous, can under certain conditions act as a distributing center for organisms that have developed a localizing affinity for particular tissues at a distance and can there produce characteristic inflammatory lesions is still a disputable problem.

The frequency of the coexistence of peptic ulcer and intraabdominal foci of infection, such as chronic appendicitis and chronic cholecystitis, is believed by many to indicate a causal relationship.<sup>45, 186, 191, 192, 208, 209</sup> It is thought that such intraabdominal foci act as a trigger release for stimuli which disturb the balance of nervous control of the pylorus, producing either a pylorospasm or achalasia with consequent gastric retention and interference with normal duodenal regurgitation.

As a result of the great number of gastric resections in the German clinics, abundant and valuable material was furnished the pathologists in their microscopic study of gastric and duodenal ulcer. The results of their investigations suggest that ulcer formation depends upon a more or less acute inflammatory process of the mucosa with resulting damage of the proteolytic action of the gastric juice. They were able to demonstrate with striking uniformity a characteristic gastritis, duodenitis, and folliculitis.<sup>210-215</sup>

#### SUMMARY

A recapitulation of the voluminous clinical and experimental investigations merely reiterates the ineluctable fact that no single factor can be held responsible for peptic ulceration in general. Undoubtedly in some instances certain factors play the most conspicuous rôles. However, these studies clearly indicate that ulcer is the result of a tessellation of factors. A physiologic comprehension of their significance is established more readily by their analysis under the classification of: (1) constitutional, (2) chemical, (3) tissue susceptibility, (4) mechanical or traumatic, and (5) infection.

In a most perspicuous disquisition of this subject, Ochsner and his coworkers<sup>216</sup> have expounded a thoroughly rational understanding of the physiologic principles involved in the development and maintenance of peptic ulceration. This concept maintains that ulcer is established by the summation of two groups of factors: (1) the *predisposing*, which may be considered as uncontrollable in the sense that they are inherently present, and (2) the *precipitating*, which are controllable, i.e., can be modified.

The first group consists of two predisposing factors: (1) tissue susceptibility and (2) constitutional. By tissue susceptibility is meant an inherent vulnerability of certain portions of the gastrointestinal tract to the digestive eroding effect of the acid gastric juice. These areas comprise the lesser curvature of the stomach (*magenstrasse*), the duodenal cap, the jejunum, and other portions of the intestinal tract which

in the wall of the ulcer. The importance of the traumatic factor has been stressed by Baggio<sup>175</sup> in experiments in which the anterior wall of the stomach was folded so as to produce an obstruction. Lesions ranging from simple erosions to typical ulcers were observed, which he attributed to the traumatic action of the ingesta and the obstruction caused by the intorflexion. Sloenmb<sup>176</sup> established partial obstruction of the duodenum in dogs, which was followed by inflammatory changes and multiple ulcers. Whereas following excision of gastric mucosa chronic ulceration of the stomach could be produced experimentally by feeding rough, irritating food, none developed during administration of non-irritating foods.<sup>177-179</sup> There is also considerable clinical evidence to support the contention that prolonged trauma of the gastric mucosa incident to foreign bodies<sup>180-183</sup> and diaphragmatic hernia<sup>184, 185</sup> may produce chronic ulceration.

Another mechanical or traumatic factor is gastric retention as a result of interference with the proper emptying of the stomach and the normal regurgitation of the alkaline duodenal secretions. Whether this is functional in the sense of spasm of the pyloric sphincter,<sup>186-188</sup> or absence of normal relaxation, achalasia,<sup>189-192</sup> or actual mechanical obstruction resulting from cicatricial contraction or tumor formation, is of more academic interest than practical importance, because the resultant effect is the same. Interference with proper emptying of the stomach operates in a twofold manner; viz.: (1) gastric retention which augments and prolongs gastric motility and gastric acid secretion, (2) prevention of normal duodenal regurgitation which is the major factor in the neutralization of gastric acidity.

#### INFECTION

The contention that ulcer formation is the result of focal, toxic, embolic, or specific bacterial influences is supported by extensive clinical and experimental investigations. Boettcher,<sup>193</sup> in 1874, is credited usually with the first demonstration of bacteria in the marginal tissue of ulcer. Since then innumerable investigators have attempted to show a definite relationship between infection and the formation of ulcer.

The results of some studies in this respect have suggested the postulation of a specific infection.<sup>194-200</sup> Probably the most enthusiastic and intransigent advocates of this factor are Rosenow and his coworkers.<sup>194, 196, 197, 201</sup> As a result of their investigations these workers contend that there exists a specificity of certain organisms for a particular type of tissue which they term "elective localization." In the case of ulcer they have been able to isolate from septic foci, such as the teeth, the tonsils, and the sinuses of patients, certain strains of streptococci which in animal experimentation reproduced lesions similar to the type from which the patient suffered. On the other hand, other investigators<sup>202-207</sup> have shown the significance of nonspecific infections. Whether a focus of

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may be exposed to acid gastric chyme, such as Meckel's diverticulum containing gastric mucosa. This innate characteristic is present in all individuals. On the other hand, the constitutional factor exists only in those individuals who develop ulcer. Although it is extremely difficult to define or state exactly what constitutes this factor, its importance and existence can no longer be denied. That there is present in certain individuals an ingrained proneness or susceptibility to gastroduodenal ulceration has been repeatedly demonstrated.

Whereas both these predisposing factors may be present in an individual, peptic ulcer does not necessarily develop. However, ulceration does occur if to this predisposition group there is added the precipitating factors. This latter group of factors consists of (1) chemical, (2) mechanical or traumatic, and (3) infection. By the chemical factor is meant a disturbance in the normal physiologic relationship of the acid gastric juice on one side and the alkaline duodenal secretions on the other which is manifested by hyperacidity and hypersecretion. The importance and significance of this precipitating factor has been repeatedly demonstrated by clinical observations and experimental investigations. The frequent occurrence of hyperacidity in patients with ulcer and the strictly limited localization of the lesion with striking uniformity in only those areas which are habitually bathed in acid chyme and in other parts of the intestinal tract only under exceptional circumstances which permit exposure to the gastric secretion have established hyperacidity and hypersecretion as preeminent factors in the development of peptic ulcer. Whether in the ulcer patient this acidity factor becomes relatively more prominent because of faulty or improper neutralization or because of overacidity due to some stimulative effect cannot be definitely stated, but its real significance can no longer be denied.

The other precipitating factors are mechanical or traumatic and infection. By the former is meant the traumatic effect of rough foods, the concept of the "magenstrasse" as the gastric pathway, and gastric retention resulting from pylorospasm or achalasia, which is conducive to hypersecretion and hyperacidity and interferes with normal duodenal regurgitation. Infection may be operative directly by producing specific inflammatory changes, or indirectly, when the focus is intraabdominal, by producing pylorospasm and consequent gastric retention.

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## THE PATHOLOGY OF GASTRIC ULCER

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THE pathologist's interest in gastric ulcer centers about three problems: (a) the cause of the disease; (b) its morbid anatomy; and (c) the functional changes associated with the presence of ulcer and the complications which may arise from it. It is our present proposal to discuss these aspects of the problem as succinctly as may be possible.

The cause of chronic gastric ulceration still remains a mystery. It is true that in certain toxic or septic conditions such as uremia or burns, small superficial acute ulcers, and hemorrhagic erosions which may become ulcers (Fig. 1) develop, but these throw little light upon the real problem of the indolent chronic ulcer. These acute ulcers, which commence as small foci of necrosis, hemorrhage, or thrombosis in the mucosal vessels, with a surrounding inflammatory reaction, may develop into shallow erosions which may extend so as to involve the muscularis and even perforate, but as a general rule they are merely transitory and unimportant lesions which heal without serious involvement of the muscular coats which leave no scar behind. Except that they may be regarded as illustrative of the initial stages of gastric ulceration of any type these multiple mucosal lesions are of little interest for our main problem and we may leave them.

The problem with which we are really concerned is that of the single chronic ulcer. It is true that we occasionally see this ulcer in its acute phase and the picture thus presented (Fig. 2) is of value since it informs us upon a stage, which we can assume generally to be a short one, through which the lesion must pass before the chronic ulcer is evolved. This stage is, however, only rarely encountered in surgically removed material, and much that has been written upon acute ulcers, especially on the statistical side, is of little importance for our present purpose since the data have been gained from postmortem material in which the lesions often represent terminal complications in those dying of other forms of disease.

Returning to our main problem, it is clear that the chronic ulcer is dependent upon quite different factors from those which occasion the multiple erosions. In the first place it is usually single; then its site in the vast majority of cases is limited to a restricted area of the stomach's surface: over long periods it shows little or no tendency to heal but,

at the same time, it may show an equal disinclination to extend. It remains a callous, indolent, unhealing ulcer. The peculiar and constant localization of the lesion to the lesser curvature, some 2 to 3 inches proximal to the pylorus, has been given special etiological significance, and it has been correlated with an assumed special exposure of this part of the stomach—the “gastric pathway”—to trauma and friction from the gastric contents, but there is little in the way of fact to aid the supposition that this is a causal factor. The greater curvature in this segment must participate equally in such traumata and the same anatomical peculiarities and yet it escapes the supposed consequences. The thrombosis of small vessels was the cause suggested by Virchow;

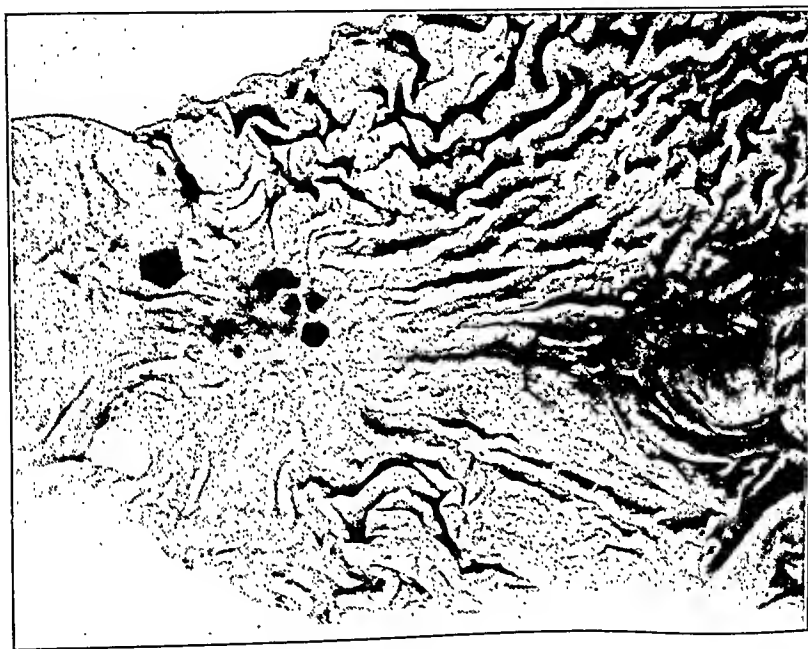


Fig. 1.—Superficial and hemorrhagic erosions in the stomach of a man dying from uremia.

but no convincing reason for such thrombosis has ever been forthcoming, and, moreover, the gastric anastomoses are so free that a limited thrombosis would be without effect. Further, no explanation has been advanced to show why a lesion resulting from such thrombosis should remain so long unhealed. True it is that extensive vascular derangement, even including complete obliteration, is to be demonstrated in the floor of the chronic ulcer, but here it is clear that such changes are the result of the ulcer and not its cause. On the experimental side it has been shown that the excision of areas of mucosa is not followed by ulceration but by healing, which is usually accomplished within the space of about ten days. When, however, as Bolton showed, the acidity of the

gastric juice is artificially increased, the healing of these lesions is delayed and chronic ulcers are produced which are similar in structure to those found in man. Constricting the pylorus has a similar effect, so that the prolonged action of acid may be regarded as a factor similar in effect to hyperacidity. It is clear, therefore, that the acid gastric juice is an important accessory factor in the production of an ulcer and in maintaining the condition of chronic ulceration: but when we have said this we have exhausted most of our exact knowledge of the part which it plays and we have left unanswered the question of why the acute ulcer so often heals, and only on occasions becomes chronic; why the chronic ulcer sometimes heals; and why the surgical lesion left after the excision of a chronic ulcer will generally heal. The main

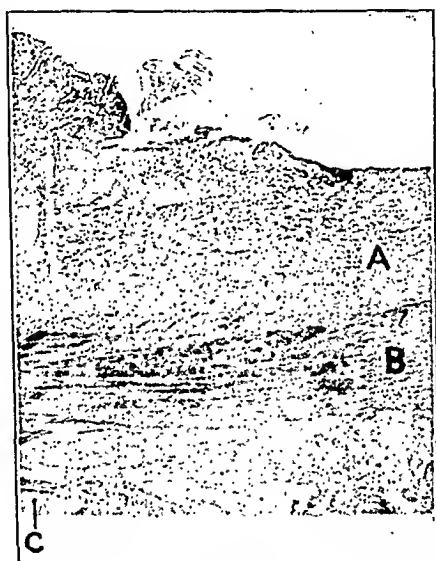


Fig. 2.—Acute ulcer. A. Edematous Submucosa. B. Circular muscle. C. Longitudinal muscle. ( $\times 12$ .)

causal factor of chronic ulcer is still unknown. It was thought at one time that an abnormal hyperchlorhydria was associated with gastric ulcer and that this might be a causal factor, but more recent investigation has dispelled this belief. The presence of an ulcer, if it cause pyloric spasm, certainly has the effect of increasing the concentration of hydrochloric acid and in prolonging its action in the stomach, as the prolonged and mounting curve of the fractional test meal will show, so that in such cases a vicious circle is introduced and the experimental requirements for chronic ulcer production are fulfilled. Once the chronic ulcer is established, the acid gastric secretion is of unquestionable importance in retarding or annulling efforts at healing and it must be held responsible, to some extent at least, for the absence of healthy

with considerable fibrosis and distortion, and (3) those involving other organs. A small ulcer of the first group is illustrated in Fig. 3. There is little or no change in the configuration of the stomach and little induration of the surrounding gastric wall, even though in the case illustrated the clinical history suggested a long duration. In microscopical section the general histology of the chronic ulcer is illustrated in Fig. 4. The mucosa overhangs the edge and ceases abruptly, being replaced by some necrotic debris which forms the floor of the ulcer. The muscular coats end more or less abruptly and a mass of hard, relatively avascular, sclerosed fibrous tissue completely interrupts the continuity of the coats of the stomach beneath the area of ulceration. On its sur-

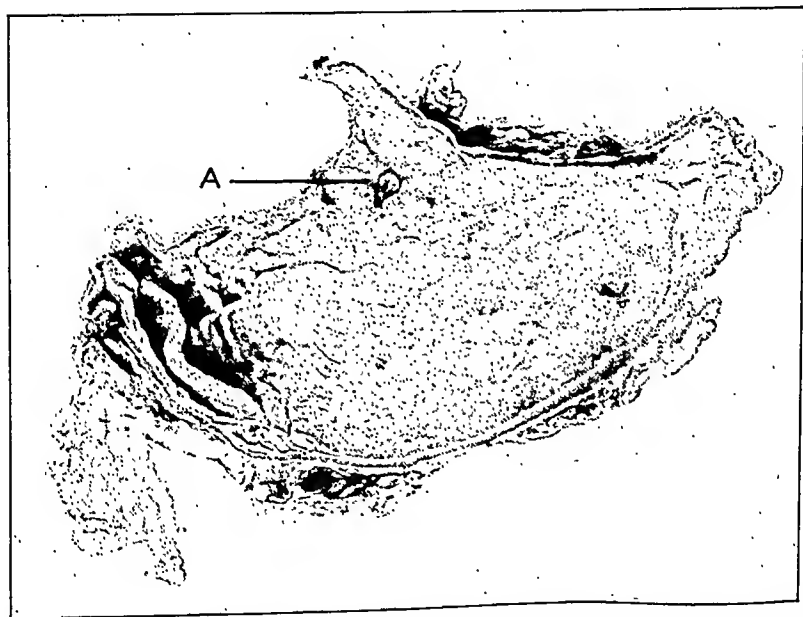


Fig. 3.—Small chronic ulcer. A. Ulcer, which is on the lesser curvature but appears on the posterior wall owing to the specimen being opened out.

face this fibrous plug appears to be undergoing a slow necrosis, as evidenced by the presence of a layer of necrotic tissue which takes acid stains strongly, and beneath this higher magnification shows some superficial fibroblastic and leucocytic reaction. On the whole, however, and generally, there is a remarkable absence of evidence either of the process of extension or of that of repair. If we examine the edges of the ulcer, we find the submucous coat is thickened and often edematous for a short distance on either side. Newcomb (1925) has drawn attention to the fusion which tends to occur between the muscularis mucosae and the subjacent muscularis if healing of the ulcer takes place. On the other hand, when a carcinoma is extending in the stomach wall, the malignant cells tend to infiltrate along this tissue plane and to split



Fig. 1.—Low power section of a chronic ulcer. Stained by van Gieson's method. ( $\times 3.5$ .)



off the mucosa and its muscularis from the underlying circular muscle (Fig. 5). To the writer the most characteristic feature of the chronic ulcer is the complete destruction of the muscular coat at its base, so that the whole thickness of the ulcer floor—from lumen to peritoneum—is composed of fibrous scar tissue. The impression which the study of such lesions strongly creates is that though the ulcer may remain static, in point of size, over considerable periods of time, yet a ceaseless inflammatory reaction of low grade is maintained with continued fibroblastic proliferation in its base and often a continued exudation of inflammatory edema fluid into the areolar tissues of the stomach wall in the neighborhood. The fibroblastic reaction is, however, insufficient to diminish the scope of the ulcer and merely balances the constant slow

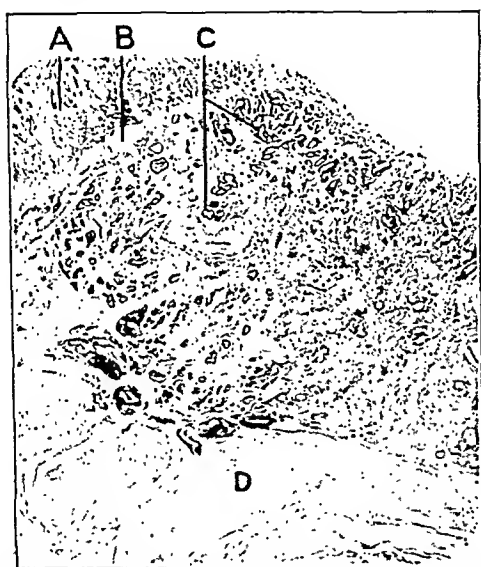


Fig. 5.—Early carcinoma spreading along the submucosa and splitting off the muscularis mucosae from the subjacent muscle. A, Mucosa. B, Muscularis mucosae. C, Carcinoma cells. D, Circular muscle. (X12.)

neerosis which goes on at the surface. At the same time the mucosal proliferation is inhibited and no extension of the mucosa into the crater of the ulcer can take place as long as healthy granulation tissue, upon which it only can engraft itself, is absent.

In the second grade of severity come those ulcers in which there is considerable distortion of the organ. This results from the spread of fibrosis beyond the stomach wall. The extent of the associated fibrosis is extremely variable and is difficult to correlate with any single causal factor. Certainly, as far as one is able to judge from clinical histories, it is not wholly, or even in the main, dependent upon duration. It is common to find well-marked fibrotic changes in the submucous coat in the area about the ulcer crater, but this sclerosis may be distributed



eccentrically, partly as a result of healing in one direction with spread in another, so that in a saddle ulcer it may affect one wall much more than the other. This is seen in a moderately developed condition in Fig. 6 which shows a partially healed ulcer of the lesser curvature with a well-marked fibrosed scar in the region of maximum change. Here there is also a considerable edematous infiltration of the submucous coat which is much more marked in the posterior wall and in which active fibroblastic proliferation is going on. Actual distortion is most usually produced by the spread of fibrosis into the gastrohepatic omentum. Figs. 7 and 8 show a common result of this fibrosis, which causes

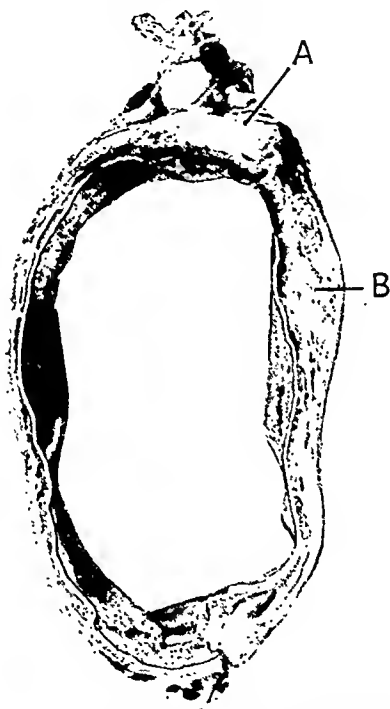


Fig. 6.—Sagittal section of the pyloric portion of the stomach at the site of a partially healed ulcer of the lesser curvature. There is a dense scar (A) at the site of the ulcer above which the sentinel gland is seen lying in the gastrohepatic omentum. There is also considerable fibrosis and edematous thickening (B) which in this case extends well down onto the posterior wall.

a puckering of the stomach wall and an approximation of the coats of the viscus on either side of the ulcer so as to produce a decided incisura upon the lesser curvature which becomes progressively deepened. In the first case illustrated the duration of the condition had been only 18 months, but in another and almost identical specimen with a similar degree of distortion the history of gastric derangement was as long as thirty years.

By the spread of fibrosis and edema towards the greater curvature, the condition of hourglass stomach (Fig. 8) is brought into being, and

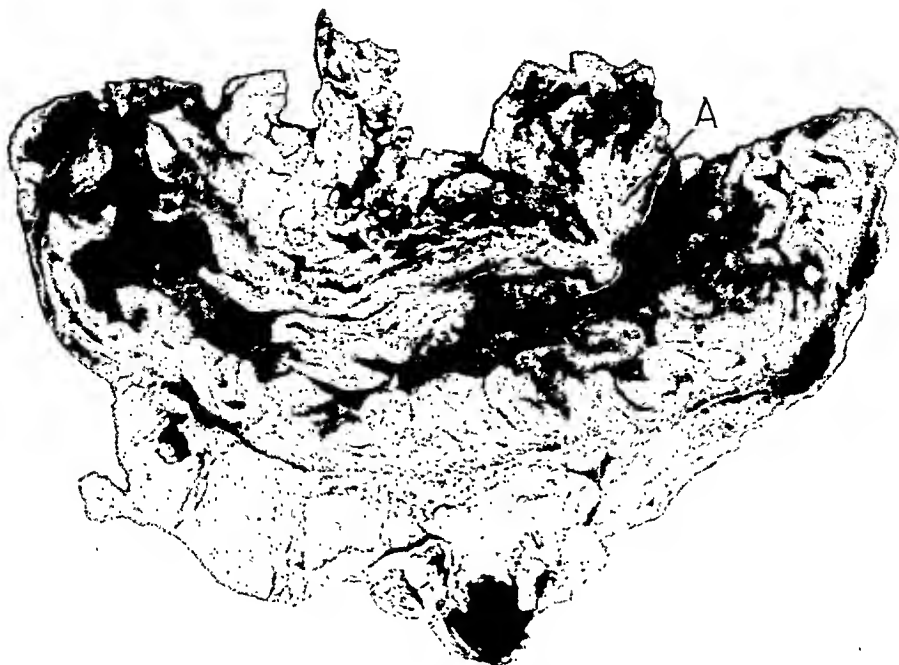


Fig. 7.—Coronal section of a stomach with the anterior wall removed. There is an ulcer on the lesser curvature which is causing complete destruction of the muscular coat and considerable puckering and indentation of the lesser curvature.

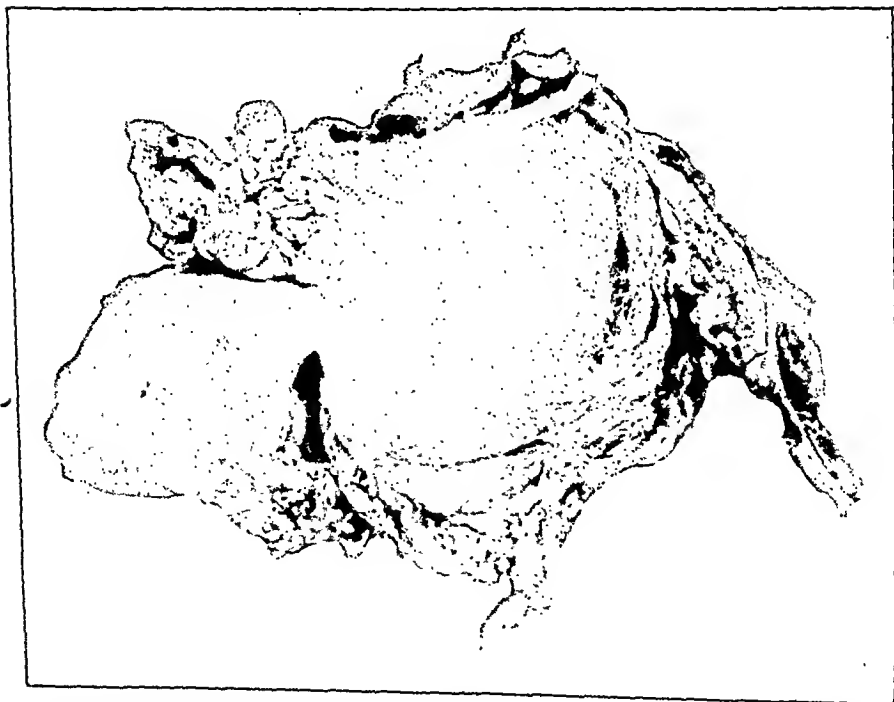


Fig. 8.—Unopened stomach seen from the front; there is a well-marked hourglass constriction; note the incisure on the greater curvature.

this is often assisted by spasm of the circular muscle fibers radiating from the ulcer region, which produces a complementing incisura on the greater curvature and tends to complete the hourglass condition. In extreme cases the whole neck of the constriction is fibrous and there is a complete organic stricture, but in the less severe grades spasm is a decided contributory feature. An extreme degree of distortion from fibrosis is illustrated in Fig. 9 which shows a very callous ulcer with an extragastric pocket which is actually encroaching upon the lesser curvature from without: there is in addition marked edematous infiltration and fibrosis of the submucosa and the omentum, and both spasm and hypertrophy of the muscle in the vicinity.



Fig. 9.—Chronic ulcer penetrating the gastrohepatic omentum and actually extragastric. Note the enormous edematous infiltration of the stomach wall and the thickening of the muscular coats.

Thirdly we have the more extensive and chronic types of ulcer which undergo considerable extragastric extension and involve related organs, more especially the pancreas and the liver. Fig. 10 shows a large ulcer penetrating the liver deeply and Fig. 11 an ulcer which is penetrating to the pancreas, the white nodular tissue of which is well seen in the ulcer floor. Such involvement may set up chronic pancreatitis. It is more especially in ulcers of this sort that the erosion of large vessels occurs giving rise to grave and sometimes fatal hemorrhage.

*The Complications of Chronic Gastric Ulcer.*—The important complications are (a) perforation, (b) hemorrhage, (c) malignancy. Both

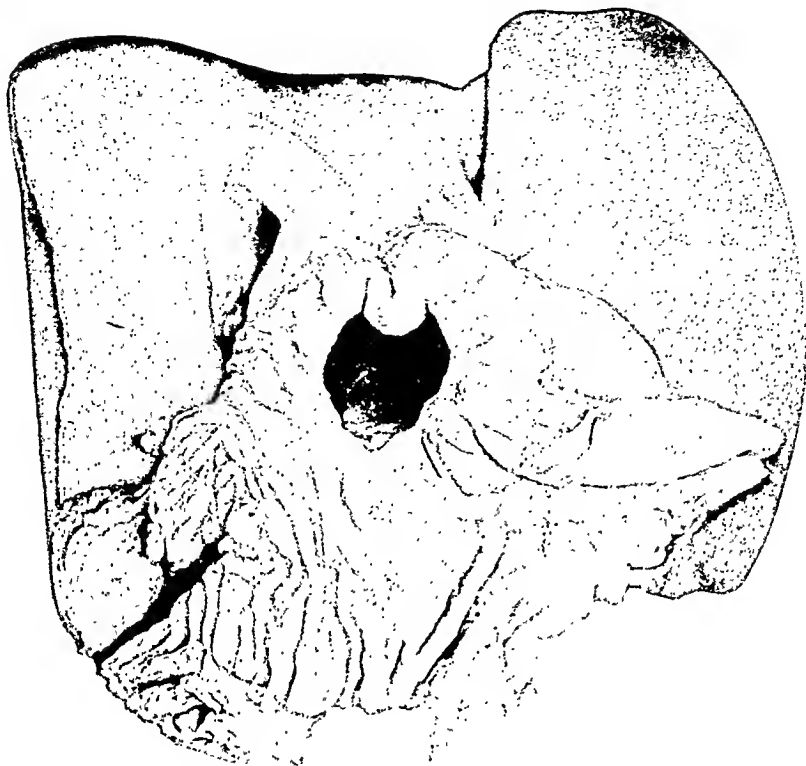


Fig. 10.—Ulcer penetrating to liver. (P.M. specimen.)

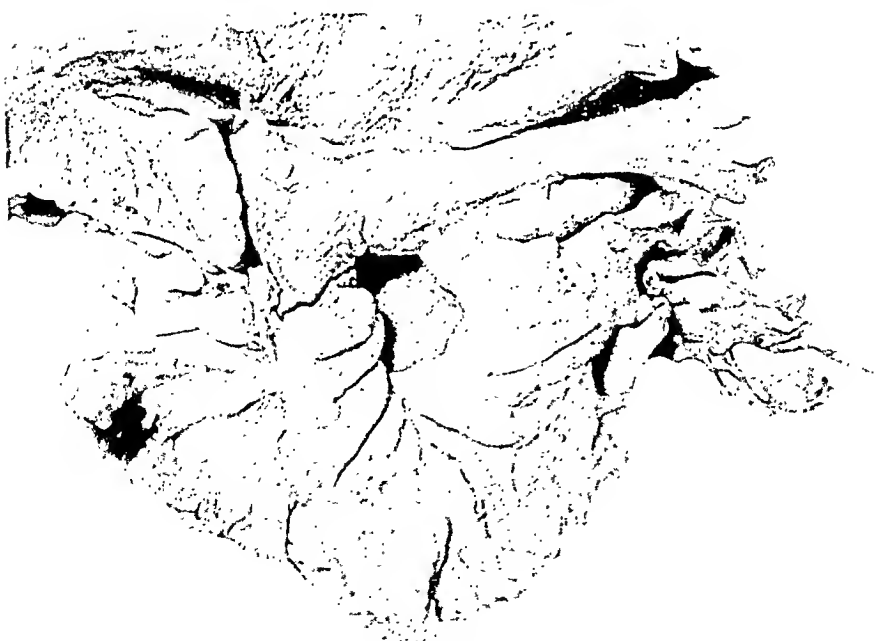


Fig. 11.—Ulcer penetrating to pancreas. (P.M. specimen.)

perforation and hemorrhage are commoner in the acute type of ulcer than in the chronic type, since in the latter the perforation is to a large extent guarded against by adhesions and the chances of hemorrhage are lessened by the protective endarterial changes which are usually



Fig. 12.—Endarteritis obliterans of vessels in the base of a chronic ulcer. (X12.)



Fig. 13.—Thrombosis of an eroded artery at the base of a chronic ulcer.

developed. The acute type of ulcer is responsible for most of those cases of profuse gastric hemorrhage which occur in young women, especially those who are the subjects of anemia. When hemorrhage occurs from a chronic ulcer, it is apt to be more dangerous and intractable for reasons which we shall explain. In any case amongst chronic ulcers it is those which are associated with the more clamant symptoms, in-

dicating an actively progressing lesion, which offer the greatest risks both from hemorrhage and from perforation.

The effect of the slow advance of an ulcerative process upon the larger vessels in its vicinity is to set up a process of occlusion by endarteritis and endophlebitis. These changes, which are irritative in origin and protective in function, are extremely common and indeed are characteristic of the histological findings in the tissues at the base of any chronic ulcer (Fig. 12). Often the process is completed by thrombosis and at a later date the organization of the thrombus, so that by the time the arterial trunk is opened it is no longer permeable (Fig. 13).

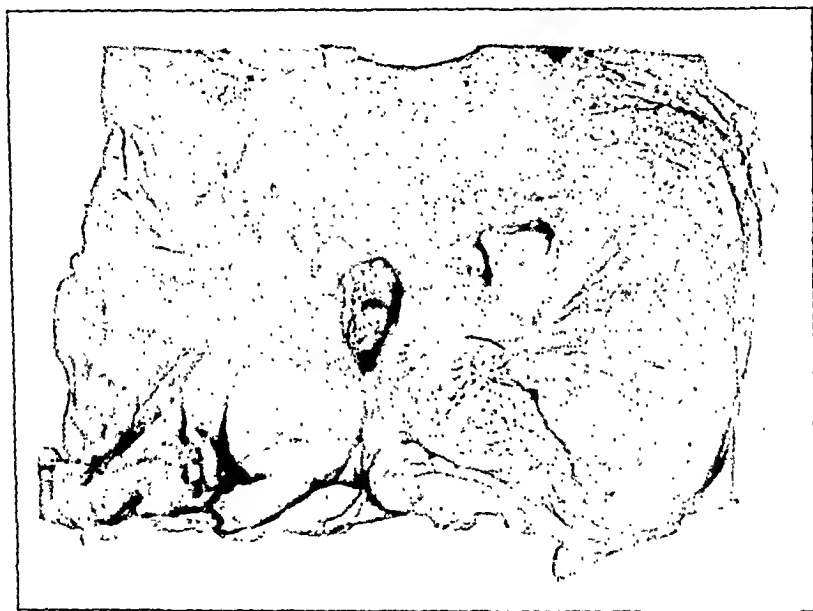


Fig. 14.—Aneurysm of the left gastric artery at the base of a chronic ulcer. A postmortem finding, rupture not having occurred. The aneurysm is seen bulging into the floor of the ulcer.

At times, however, the reaction fails, either on account of the rapidity of the arterial ulceration or from causes which are unknown, and relatively large and unoccluded vessels may be invaded. When this happens there is a tendency for the artery to become aneurysmal and to rupture into the base of the ulcer (Fig. 14). In such cases the hemorrhage which results is apt to be particularly intractable for the reason that the artery is held in rigid sclerous fibrous tissue and is not only incompletely severed, the rupture being lateral, but is also prevented from retracting by the adherence of the fibrous tissue in which it is embedded. The vessels most commonly involved are the right and left gastric (coronary) arteries of the stomach, or the splenic artery which may be

eroded by an ulcer penetrating the posterior wall of the lesser curvature and involving the pancreas, at the upper margin of which this vessel lies.

*Perforation.*—This, as we have already said, is commoner in the acute than in the chronic type of ulcer and when it occurs in the latter, it is due to unusually active progress and is therefore most liable to appear in those ulcers which are giving rise to active symptoms. The actual perforation is due to the rupture of a necrotic patch in the base of the ulcer which may be either central or eccentric and produces a circular hole situated as a rule on the anterior wall of the viscus. The figures collected by Stewart, and including his own extensive series, show that perforation of the anterior wall is about six or seven times as common as perforation of the posterior wall. The same observer also points out that it is most frequently ulcers of the pylorus or prepyloric regions which perforate; in his series this complication being twice as common in ulcers which lay within two inches of the pylorus as it was in those situated more proximally.

The stomach contents are in most cases from a practical point of view sterile. They cannot be regarded as bacteriologically sterile, but organisms are few in number and pathogenic forms neither frequent nor virulent: in consequence the peritoneal shock and peritonitis which follow upon perforation are traumatic and chemical at their inception, and it is only after a period, which has been put at about twelve hours, that a bacterial flora begins to establish itself in the peritoneum and an infective peritonitis sets in. This explains the supreme influence which early operation has upon the prognosis.

*Malignant Change.*—The frequency of this complication in gastric ulcer has been actively debated and widely divergent views have been expressed. Our own view as a result of pathological, clinical and histological studies, (Dible, 1925) is that in only a small proportion of cases—probably about 5 to 6 per cent—is carcinoma to be attributed to ulcer. The development of malignancy unquestionably occurs—as it may occur in any chronic unhealing lesion—and it may *a priori* be anticipated with greater frequency in a lesion constantly exposed to infection and the irritation of the gastric juice, but the examination of a very large number of gastric ulcers and cancers has convinced us that there can be no hesitancy on the part of an experienced pathologist in recognizing malignancy when it is present and, further, that the signs of pre-existing ulcer—always supposing that the malignant disease has not advanced to a stage at which histological criteria are masked—are in all but an insignificant minority of cases readily recognizable. The chronicity and long history of gastric ulcer, the short history of carcinoma; the predilection of ulcer for a site 2 to 3 inches from the pylorus and of cancer for the juxtapyloric position; the earlier age of onset; together with the histological criteria, indicate that in general

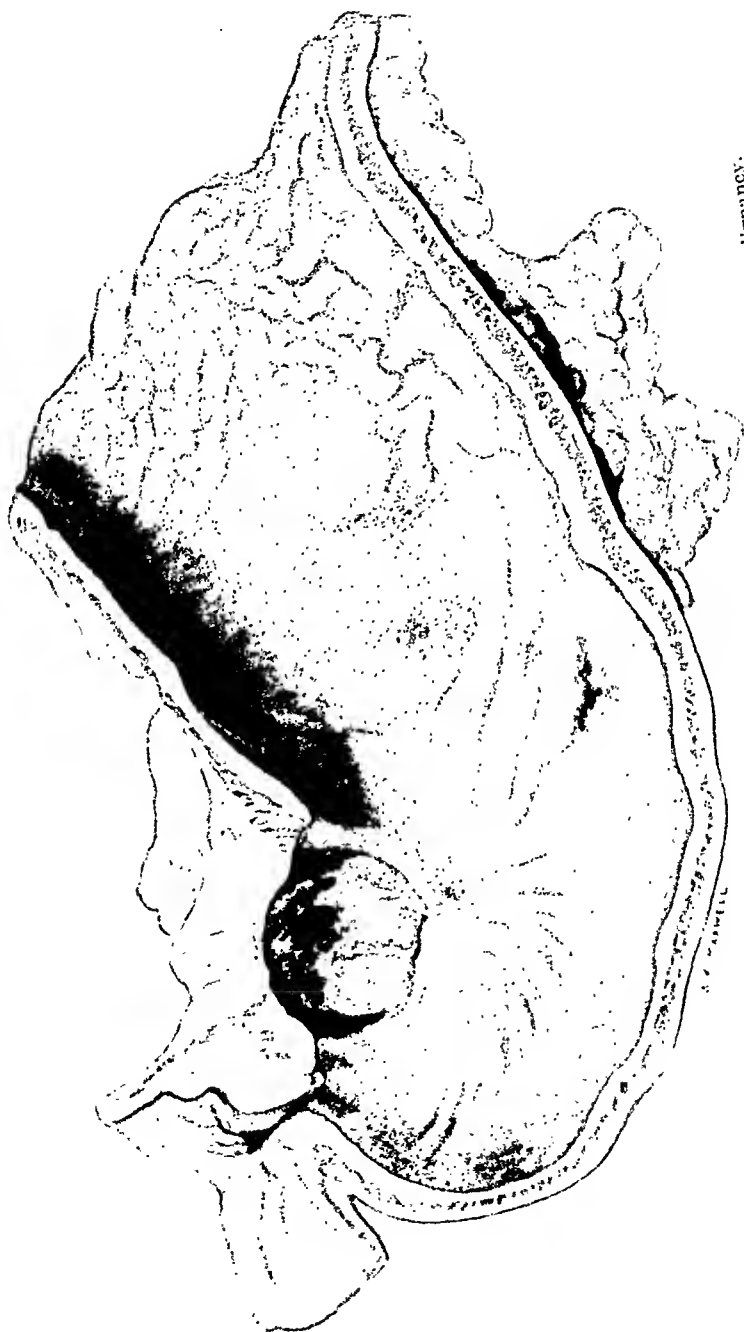


Fig. 15.—Ulcer-cancer. There is nothing in the naked-eye appearance to denote malignancy.





the diseases are distinct and independent. Briefly put, the histological criteria of ulcer are: the complete destruction of the muscular coat and its replacement by fibrous tissue; the well-developed endarteritis and endophlebitis in the juxtaposed vessels; and the presence of simple scarring as opposed to malignant stroma reaction in the stomach wall: all of these are features of chronic ulcer. Some of these changes are also produced by the action of a malignant neoplasm, especially where this is of a type productive of an abundant stroma, but where all data are considered, clinical and pathological, the number of cases in which the balance of evidence points to malignant disease having arisen in a chronic ulcer is but small, and in our experience of the order of 5 to 6 per cent. Finally, it should be emphasized that the observer must not be led astray by superficial appearances and the mere semblance of ulcer, which it is very obvious may occur with the greatest readiness in the ill-resisting tissue of a neoplasm.

A typical example of ulcer-cancer is illustrated in Fig. 15.

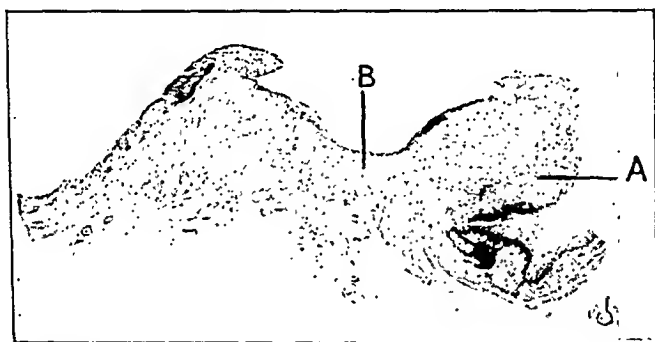


Fig. 16.—Microscopical section of ulcer-cancer illustrated in Fig. 15. A. Duodenal mucosa. B. Fibrous tissue permeated by cancer cells. ( $\times 2$ .)

This patient was a male, aged twenty-nine. There was a history of gastric symptoms of about twenty years' duration which were latterly more severe and accompanied by almost constant pain. Partial gastrectomy was performed by Professor A. H. Burgess, of Manchester, and revealed a chronic ulcer of the lesser curvature close to the pylorus. A large section in the coronal plane (Fig. 16) shows the general features of ulcer under the lower power, but under the higher magnifications extensive infiltration with cancer cells is seen and a secondary deposit was present in a sentinel gland close to the base of the lesion. The interruption of the muscular coat by a fibrous cicatrix was complete, and it is important to note that considerable areas of this scar tissue showed an entire absence of cancer cells. The vessels showed moderate endarteritis. The growth was a rather anaplastic columnar-celled carcinoma giving rise to a moderate stroma reaction.

*Healing.*—The majority of acute ulcers heal; only a certain proportion become chronic, and a considerable number of these heal. Exact figures are impossible to obtain, but the regularity with which cure follows upon the satisfactory and persistent treatment of acute ulcer

with hematemesis points to the eminent curability of the lesion at this stage. From the morbid anatomical point of view ulcers which do not involve the muscle will heal completely, even to the regeneration of the muscularis mucosae and will therefore fail to leave recognizable scars or, at the most, will leave only very trivial alterations not easy to detect. From the rarity of scars which involve only a portion of the muscular coat, it must be rare for acute ulcers (as distinct from erosions) to heal at the stage of partial muscular destruction: so that when once the muscularis has been attacked it would seem that the ulcer either passes on to complete muscular destruction with perforation or goes through the stage of being a chronic ulcer before healing takes place. The presence of scars which have a complete epithelial covering



Fig. 17.—Healed ulcer. A. Muscle remnants. B. Fibrous tissue. C. Artery showing persistent endarteritis. (×12.)

over a fibrous cicatrix, which wholly interrupts the continuity of the muscularis, is a common finding at postmortem examinations and represents a healed chronic ulcer.

The possibility of healing in a chronic ulcer would appear to be largely governed by the amount of distortion which it has caused. It is difficult to imagine a gross and callous lesion such as that depicted in Fig. 9 ever healing, while there are no reasons to doubt that a small ulcer such as that depicted in Fig. 3, in which there is no anatomical obstacle to epithelialization might, given favorable circumstances, heal.

The healing ulcer is recognized by a clean floor devoid of sloughs and a generally sloping margin down which a thin single layer of epithelium is creeping onto the ulcerated surface. The evidences of acute reaction are at the same time redness and the edema which is partly responsible

for the overhanging edges of the typical ulcer subsides. The fibrous tissue in the floor also becomes less edematous and better organized and contracts, often to a marked degree, so that the final cicatrix is almost trivial when healing is complete (Fig. 17). As this matures the epithelial covering becomes more complex and in the healed state there is a certain restoration of the normal glandular structure of the mucosa, which however always falls short of perfection, since it is usually rather flattened and there is no regeneration of oxyntic cells. It is also not uncommon to find that the partially obliterated arteries which are so common in the gastric ulcer persist after healing is complete.

Taylor (1927) and Stewart point out that it is quite common for areas of the regenerated epithelium to undergo a form of heteroplasia leading to the production of goblet cells and a superficial resemblance to intestinal epithelium.

My thanks are due to the *British Journal of Surgery*, the proprietors of which have kindly allowed the reproduction of many illustrations from the paper published therein in 1925.

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# THE VALUE OF GASTROSCOPY IN DIAGNOSIS AND SURGICAL TREATMENT OF CHRONIC GASTRODUODENAL ULCER

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THE following discussion on the value of gastroscopy in diagnosis and treatment of chronic gastroduodenal ulcer is based essentially on the observation of 66 patients with gastric ulcer, in whom 137 gastroscopies were carried out. Thus, on the average, every patient suffering from gastric ulcer had 2 gastroscopies done; in reality, naturally, many patients had only 1 gastroscopy; whereas, others had from 5 to 13. About the same number of patients with duodenal ulcers had gastroscopic examinations, but exact figures are not available, because it is certain that many such cases had gastroscopies without my knowing it. From 1921 to 1932, a large number (about 120) of gastric ulcers were examined by the old rigid Schindler gastroscope. They are not included in the following discussion.<sup>1</sup>

The section on postoperative stomach is based on the findings in 117 gastroscopies carried out with the flexible gastroscope in patients who had undergone some operation because of gastroduodenal ulcer.

The paragraph on gastrophotography is based upon 76 examinations with the gastrophotor and on 96 gastroscopic examinations in which the rigid gastroscope with Hennings camera attachment was used. That on radiography refers to over 4,000 x-ray relief examinations carried out with Sielmann, Munich, from 1926 to 1934. In 360 cases examined after the invention of the flexible gastroscope, comparison with the gastroscopic picture was possible.

It is assumed that the reader does not fully know the rapid development of modern gastroscopy since the invention of the flexible gastroscope; therefore, a few brief statements on the technical part shall be given.

The flexible gastroscope is a round tube, consisting of the lower flexible and the upper rigid parts. The lower flexible part, which bends during the examination along the posterior wall of the stomach, remains flexible and bent during the whole examination. Its upper end lies still above the hiatus esophagus, even if the instrument is introduced to its full length. The flexible part is elastic and is guided by an elastic rubber tip. Above this rubber finger is a very bright electric lamp which illuminates the stomach and the objective which collects the rays coming from the gastric wall and which deviates this picture into the axis of the gastroscope. The sharp and bright picture then is observed

through the ocular. This instrument is introduced into the stomach of the patient in his left side position exactly like a simple Ewald tube, but after a careful local anesthesia of the throat. This makes the procedure easy for any reasonable, cooperative patient. Because of the small diameter of the instrument (7.5 mm.) one frequently experiences that the patient not only is willing to allow the physician to observe the course of the ulcer by repeated gastroscopies, but even desires frequent repetition of the examination. The mode of introduction has to be learned; however, it is not difficult. In contrast, the orientation in the cavity of the stomach and the interpretation of the seen picture are very difficult. Gastroscopy is not like other endoscopies. The correct interpretation of pictures in functionally so important an organ is only possible either by a specialist in internal medicine or by a surgeon well trained in general surgery. Both must have a good knowledge in pathologic anatomy.

At the outset it should be stated frankly that in ulcer gastroscopy has not the undeniable outstanding value that it has in the two other major diseases of the stomach, namely, carcinoma and chronic gastritis. The reason is that many ulcers cannot be seen, while carcinoma and the various forms of chronic gastritis almost always are seen. After this concession, the author will attempt to show that in chronic gastroduodenal ulcer, gastroscopy is of great value, especially to the surgeon.

The discussion will be subdivided as follows: (1) the gastroscopic findings in chronic gastroduodenal ulcer will be described; (2) the differential diagnosis of the various types of gastric ulcerations will be discussed; (3) the gastroscopic findings in postoperative stomachs will be described; (4) a short comparison between gastroscopy, gastrophotography, and x-ray examination in ulcer will be given; and (5) the summary briefly will show the value to the surgeon of gastroscopy in gastroduodenal ulcer.

#### GASTROSCOPIC FINDINGS IN CHRONIC GASTRODUODENAL ULCER

1. *General Disturbances in the Stomach of Patients Suffering From Gastroduodenal Ulcer.*—Sometimes by gastroscopic examination the stomach of patients suffering from chronic gastroduodenal ulcer, except for the ulcer itself, appears to be normal. In many cases, however, changes are observed which are of practical importance. Some of these characterize the "ulcer stomach." They should be subdivided into: (a) disturbances of motility, (b) disturbances of secretion, (c) disturbances of circulation, and (d) inflammatory changes.

A. *Disturbances of motility:* Often it is difficult for a beginner to perform gastroscopies in patients suffering from ulcer because of the increased spasticity. While usually the passage through the esophagus is easy when speedily carried out, difficulties begin as soon as the instrument touches the posterior wall. A marked resistance is felt render-

ing it impossible to push the instrument forward and into the lower depths of the stomach. This resistance is due to a spasm of the gastric muscularis. It may be so marked as to grasp the instrument, but it subsides slowly. In a patient who had six gastroscopies, such a spasm complicated each attempt to find the suspected ulcer. By diverting the patient's attention and conversing with others in the room, it always became possible to push the instrument forward because the resistance suddenly subsided. This sudden relaxation of the gastric wall is very common in ulcer. Localized spasms near the ulcer or distant from it were frequent during the era of the rigid gastroscope. They have disappeared almost completely since the use of the flexible gastroscope. This fact, also noted by Montier,<sup>2</sup> has found no adequate explanation.

*B. Disturbances of secretion:* While the mucosa of the normal, gastritic, and carcinomatous stomach can generally be easily observed, this may be difficult in ulcer. A few moments after the introduction of the instrument, abundant secretion may begin, so that the mucosa rapidly becomes covered with secretion mixed with air bubbles. The search for the ulcer becomes very difficult, and the objective of the gastroscope needs frequent wiping by turning it to the posterior wall. This abnormal irritability is often still present when the ulcer has been healed for long months. Because of this supersecretion, the gastroscopic examination in these cases must be made rapidly, and consequently it is frequently difficult to demonstrate the ulcer to onlookers.

*C. Disturbances of circulation:* These are the most frequent and most important ones. Of all gastroscopists, however, only Chevalier Jackson and Borland have confirmed these observations. It is easy to see these changes if patients with stomach ulcers have repeated gastroscopies. Three lesions may be seen which are related to each other: mucosal hemorrhages, pigment spots, and hemorrhagic erosions. They are often seen years after the complete healing of an ulcer, and can mean, like persisting irritability, that the stomach still is ready to develop a new ulcer.

The mucosal hemorrhages, which are easily demonstrated, lie in normal, uninflamed mucous membrane. They appear as dark red patches and are pinhead to pea sized, round or linear. Frequently they are seen one centimeter above the angulus on the lesser curvature, i.e., at the most common site of gastric ulcer. Sometimes many of them lie in a row along the lesser curvature from the cardia to the angulus. If one gets the opportunity to observe such a stomach once weekly, he will find that these hemorrhagic spots are changed into brown pigment spots. These latter often are not as round as the hemorrhages, but starlike. Frequently pigment spots are found at the first examination without any hemorrhage present or together with hemorrhages.

Occasionally a hemorrhage develops into a hemorrhagic erosion. This is the hemorrhagic erosion of the older pathologists. (Fig. 1.)

Recent workers have contended that it does not exist. It is impossible to overlook them, however, if regular gastroscopic examinations over long periods of time are made of stomachs with ulcers. The erosion surrounded by a dark red area usually is not very deep; its color is gray or reddish gray. This hemorrhagic erosion seems to be the acute stage of the chronic ulcer; therefore, the expression "preulcerous conditions" may be used for the changes described in this paragraph.

*D. Inflammation in the ulcer stomach:* Gastric ulcer may be found in an apparently normal mucosa. In many instances, the adjacent surroundings of the ulcer are inflamed, swollen, edematous, or thickened. Inflammation of the whole gastric mucosa occurs, although rarely. Hard to explain are those cases in which the neighborhood of the ulcer is normal while a distant area is markedly inflamed.

In duodenal ulcer sometimes no sign of inflammation can be found, notably not the so-called ulcerative antrum gastritis. This serious dis-

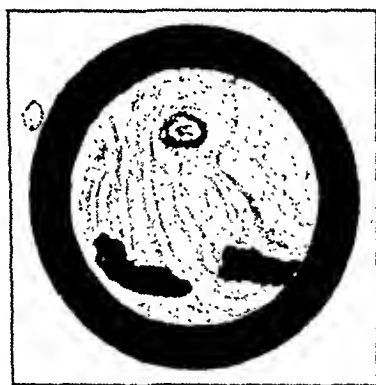


Fig. 1.—Hemorrhagic erosion. Two large brown pigmented spots are seen in the anterior wall. A small erosion surrounded by a hemorrhagic halo lies in the lesser curvature. (The black circle at the edge of gastroscopic pictures indicates the position of the objective in left side position of the patient.)

ease, though rare, exists, and its characteristic changes are easily recognized gastroscopically, but it is not found in association with duodenal ulcer. Neither has gastritic ulceration, even when checked by repeated gastroscopies, been observed to develop into true chronic ulcer. The theory of the gastritic origin of gastric ulcer (Konjetzny, Hurst, Faber) cannot be corroborated by gastroscopic observations, because: (1) too often ulcer occurs in a perfectly normal mucous membrane without any evidence of accompanying gastritis; and (2) gastroscopically, those ulcers of the frequent ulcerative body gastritis, or of the rare ulcerative antrum gastritis, have never been seen to develop into true gastric ulcers when observed over a long period of time.

When obstruction at the pylorus is present, a severe edematous gastritis, especially of the antrum, will be seen. It heals after gastroenterostomy. Although not checked statistically, I have the impression that generalized gastritis is not rare in duodenal ulcer. It may be due



to pyloric spasm which frequently accompanies duodenal ulcer, causing retention. This type of inflammation— inflammation by retention—evidently does not belong to the gastroscopic signs of the ulcer stomach.

2. *Duodenal Ulcer*.—Duodenal ulcers never can be seen with the gastroscope. In favorable cases, it is possible to see portions of the duodenum through the open pylorus, but so much shadow is cast that it is impossible to recognize details. The stomach of a patient suffering from duodenal ulcer, however, often presents the signs of an ulcer stomach, as described in the previous section (1).

The activity of the pylorus, when duodenal ulcer is present, usually is quite normal. The shortening of the antrum, the waves migrating over the antrum, the closing of the pylorus with a stellar form is as regular as in a healthy stomach. Even obstruction of the duodenum does not affect the regular normal action of the pylorus.

3. *Ulcer of the Pyloric Channel*.—Ulcer of the pyloric channel can never be seen gastroscopically. There is a decided difference, however, in the findings in cases with ulcers in this location and in those with duodenal ulceration. In cases with ulcers of the pyloric channel, usually the pylorus remains completely hidden from view, and not even that edge which is adjacent to the greater curvature can be seen. It is well known that the expert examiner is almost invariably able to see the pylorus through the flexible gastroscope with the patient lying on his left side. This is only possible because the pylorus is very mobile and in this position is adjacent to the anterior abdominal wall. If the pylorus is held by adhesions to the right side of the spine, then the spine is between the objective of the instrument and the pylorus, so that the latter remains hidden from view. It seems that in most cases with ulcer of the pyloric channel, adhesions are present, fixing the pylorus to the posterior wall of the abdominal cavity. This fact is especially important in cases with obstruction.

It frequently happens that in pyloric obstruction, which so often accompanies ulcer of the pyloric channel, the most refined x-ray relief compression technique is unable to differentiate between malignant and benign obstruction. With gastroscopy this seems to be easier. An obstructing tumor can always be brought into view through the gastroscope and can scarcely be mistaken for anything else. Perhaps the diffusely infiltrating tumors without any elevation and without any ulceration may occasionally cause difficulties. The pylorus obstructed by ulcer, on the other hand, almost never is seen through the gastroscope. Even if the antrum is observed over a long period of time, there are only slight peristaltic waves, and none of them brings the pylorus into view.

In the only patient with pyloric obstruction due to ulcer of the pyloric canal, in whom I could see the pylorus, it appeared as a pinhead-like, completely round hole in the background of the antrum. The

antral mucosa had the swollen appearance usual in obstructions. Operation and microscopic examination proved the correctness of the gastroscopic diagnosis.

4. *Prepyloric Ulcer*.—After 1,173 gastroscopies had been carried out with the flexible gastroscope, I saw my first true chronic prepyloric ulcer. This rarity of gastroscopically seen prepyloric ulcers may be due to three different reasons: (1) Probably prepyloric ulcers are not frequent. Holmes and Hompton<sup>3</sup> in their careful statistics have shown that the site of the great majority of all ulcers is the duodenum and the lesser curvature of the body, especially around the angulus. In their opinion, each prepyloric ulcer must be suspected to be malignant. Other authors (Sarah Jordan, W. L. Palmer) believe that benign prepyloric ulcer occurs, although rarely. (2) Also in prepyloric ulcer, just as in ulcer of the pyloric canal, the pylorus may be drawn backward by perigastric adhesions, and thus remain hidden from view. (3) The lesser curvature of the antrum is the most important blind spot in gastroscopy. Frequently it can be observed only during peristalsis of the antrum (Borland), but in the majority of the cases, it remains hidden from view behind the angulus. Since the portion directly adjacent to the pylorus, however, is usually seen, this third reason seems the least important for the infrequent observation of prepyloric ulcers through the gastroscope.

5. *Gastric Ulcer*.—A few gastric ulcers are not seen when lying in so-called blind spots, otherwise the gastroscopic picture of gastric ulcer is of unexpected brilliance. There is a variety of nuances in color such as one never sees in the gross specimen. The observation of a chronic gastric ulcer, therefore, is most fascinating for the beginner in gastroscopy, as well as for the expert. In the gross specimen, the stream of circulation is interrupted. All of the gastric mucosa appears to be the same grayish pink. In gastroscopy, a multitude of colors are observed, ranging from brilliant white over grayish white, yellow white, yellow brown, pink, and red to the dark red of freshly oozing blood.

A. *The edge of the ulcer*: The edge of the ulcer invariably is absolutely sharp. It may be ragged or irregular, but the limit between the ulcerated surface and the surrounding mucous membrane always is seen distinctly. Whenever there is some blending of the ulcerated area with the surroundings, malignancy can be assumed with certainty. Sometimes there are small polypoid islands of still intact mucosa near the edge; they are also sharply defined. Frequently some portions of the edges are undermined for varying extents.

B. *The floor of the ulcer*: In the majority of cases, the floor of the gastric ulcer, as seen gastroscopically, has a definite brilliant yellowish color. This color is unexpected and most striking for the inexperienced examiner. Its origin has not been fully explained, but it may be assumed that the ulcerated surface is covered by a fibrinous layer. In

rare cases, the floor is brownish or dark red. While formerly this red ulcer was believed to be a healing stage, we now know that healing ulcers remain yellow until the last moment of epithelization. The red ulcer proves that a small hemorrhage has preceded the examination. These ulcers bleed easily, and sometimes a small river of blood can be seen oozing from the red ulcer to lower parts of the stomach. Gastrosopy cannot cause any bleeding. Sometimes the blood oozing from the center of the floor flows toward the lowest part of the crater, which is often not the center, and forms a brown pool there. The complete epithelization of the ulcer can be determined only by gastrosopy. The roentgenologic crater may disappear, but gastrosopy may reveal that the ulcer is present still, shallower, but not healed. Complete epithelization may require as long as two months after the complete disappearance of the niche, even when examined by the most refined x-ray compression,

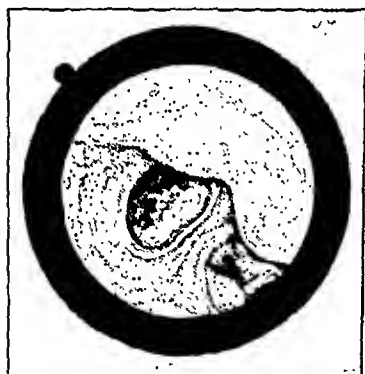


Fig. 2.



Fig. 3.

Fig. 2.—Penetrating ulcer. Large penetrating ulcer, lesser curvature. Sharp edge. Blood oozing from the center of the crater to its lowest portion. Tremendous inflammation of the adjacent posterior wall. At 5 o'clock the antrum is seen. Case checked by operation.

Fig. 3.—Gigantic penetrating ulcer. Posterior wall. Edge sharp. Floor formed by pancreatic lobuli. Benignity proved by course.

relief technique. This fact can become important in cases in which gastric surgery is considered.

C. *Penetration*: Chronic penetration of an ulcer is no contraindication to gastrosopy. It is not always possible to diagnose chronic penetration by the gastroscopic picture. In a case (Fig. 2) with a very deep craterlike benign ulcer, the floor was yellow and smooth, with some blood oozing from the center of the crater and with the surroundings badly inflamed. Operation demonstrated that the ulcer had penetrated the whole gastric wall and was covered by thickened layers of omentum. In contrast, the fact that an ulcer has penetrated into the pancreas may easily be detected with the gastroscope. The floor then is formed by the nodular-like lobuli of the pancreas which in the gastroscopic picture have a greenish gray color and which are uniform in size. This fact,

together with the sharp edge of the ulcer, prevents the examiner from wrongly diagnosing a carcinoma. (Fig. 3.)

It scarcely is necessary to emphasize that in cases of imminent free perforation of an ulcer with fever, local pain, and abdominal rigidity gastroscopy is contraindicated. Until now no perforation of an ulcer has followed the inflation of air through the gastroscope. In this respect, x-ray examination seems to be the more dangerous, since a number of perforations have been described following the palpation of the stomach during fluoroscopy of the stomach. Perforation of an ulcer following gastroscopy, however, would probably be much less dangerous than that following fluoroscopy; because in the former, the stomach would be entirely empty, whereas, in the latter, it would be filled with barium. The question might even arise whether conservative medical treatment in a case of ulcer perforation following gastroscopy would not be preferable to operation. I believe that operation would be safer and should



Fig. 4.—Perigastritis. White area in center is the ulcer. Three folds converge to its edge from 9 o'clock. At 2 o'clock the open pylorus. At 4 to 5 o'clock the musculus sphincter antri. Between ulcer and sphincter antri pouch due to perigastric adhesions.

be performed immediately. In such a hypothetical case, it would be difficult to separate exactly coincidence and cause. Montier described a case of a man who was scheduled for gastroscopy in the morning; during the preceding night he had a spontaneous perforation of the ulcer. Had this same perforation happened twelve hours later, gastroscopy would have been held responsible for the mishap.

*D. Perigastric adhesions:* It has been pointed out that perigastric adhesions are chiefly responsible for gastroscopic nonvisualization of pyloric ulcers and especially of benign pyloric obstructions. In gastric lesions, also, the gastroscopic diagnosis of adhesions sometimes becomes possible. The stomach may be distorted so much that the usual rules of orientation become useless. In a patient with a benign ulcer just above the angulus in whom six gastroscopies were done, we found in each examination a large outpouching in the anterior part of the angulus

rare cases, the floor is brownish or dark red. While formerly this red ulcer was believed to be a healing stage, we now know that healing ulcers remain yellow until the last moment of epithelization. The red ulcer proves that a small hemorrhage has preceded the examination. These ulcers bleed easily, and sometimes a small river of blood can be seen oozing from the red ulcer to lower parts of the stomach. Gastroscopy cannot cause any bleeding. Sometimes the blood oozing from the center of the floor flows toward the lowest part of the crater, which is often not the center, and forms a brown pool there. The complete epithelization of the ulcer can be determined only by gastroscopy. The roentgenologic crater may disappear, but gastroscopy may reveal that the ulcer is present still, shallower, but not healed. Complete epithelization may require as long as two months after the complete disappearance of the niche, even when examined by the most refined x-ray compression,

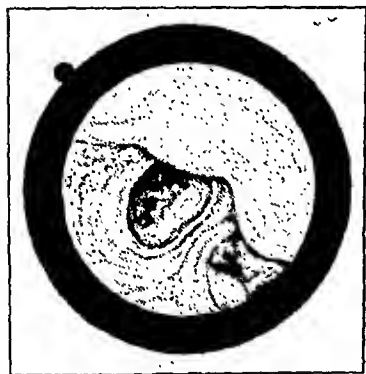


Fig. 2.

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often the surgeon opens the abdomen without being able to find the source of the bleeding. If, gastroscopically, bleeding from a gastric lesion has been excluded, hemorrhage from duodenal ulcer may be assumed and the patient operated upon. Gastroscopy is carried out so easily and quickly that it can be performed even in very weak patients. The washing out of the stomach with ice water has to be carried out on a table which permits Trendelenburg position. The stomach must be emptied speedily after quick good local anesthesia of the throat, or even, if necessary, under general anesthesia. An expert can perform the gastroscopy in one minute. Then the surgeon may go ahead with the operation or abandon it, according to the gastroscopic findings.

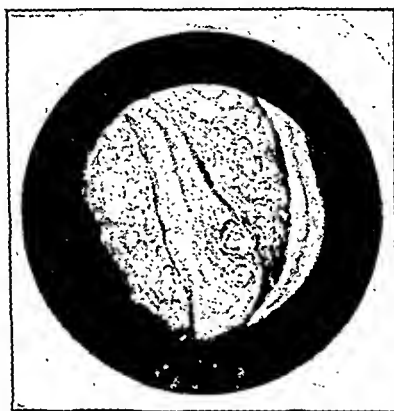


Fig. 5.—Chronic hypertrophic ulcerative gastritis. Two gastric folds. In the left one, an ulceration surrounded by a red area. In the valleys between the folds, nodular excrescences.

#### GASTROSCOPIC DIFFERENTIAL DIAGNOSIS OF THE VARIOUS TYPES OF GASTRIC ULCERATIONS

It cannot be the aim of this paper to give a description of the gastroscopic aspect of the various gastric diseases leading to ulceration. The differential diagnostic criteria, therefore, shall be mentioned only briefly.

1. *Hemorrhagic Erosions*.—They have been described above. They always are seen in a noninflamed normal mucosal area. They are gray, shallow; the border is hemorrhagic. Frequently multiple mucosal hemorrhages and pigmented spots are found in the lesser curvature. Sometimes a real chronic ulcer is present in the same stomach or in the duodenum of the same case.

2. *Erosions of Chronic Superficial Gastritis*.—These are small, often only pinheadlike. They sometimes can be diagnosed only because a high light sliding over the erosion vanishes for a moment during the respiration. Sometimes they have a small, red border. The surroundings are superficially inflamed, presenting adherent layers of mucus, red patches, and edema. These erosions heal quickly.

(Fig. 4). This pouch was not like a spasm or like a diverticulum. It could be explained only by assuming tension perigastric adhesions around the ulcer. Since no operation was performed, however, no proof was possible.

*E. Organic hourglass stomach:* The spastic narrowing of the stomach, often seen in x-ray examination, disappears in the gastroscopic examination. True organic hourglass stomach in which the tissues of the stomach are narrowed by scars seems to be rare. I saw only one case in the series used. I performed a gastroscopy on a colored woman in the gastrointestinal department of the General Hospital, Cincinnati, whose x-ray picture showed an hourglass formation. The gastroscope penetrated into the upper bag. There a diverticulum formation was seen. In its background was a small dark oval hole, the entrance into the lower bag. All parts of the mucosa were smooth. This patient, however, had a positive Wassermann reaction and had been treated for syphilis. I believe that many cases of organic hourglass stomach are due to gastric syphilis.

*F. Gross hemorrhage:* Gross hemorrhage is one of the most important indications for gastroscopy. Most hemorrhages nowadays are treated medically; in such a case, gastroscopy may be delayed until the danger is over. The postponement should not be too long, for it is well known that x-ray examination, if delayed a few weeks, frequently fails to reveal the source of the bleeding. The bleeding, however, may have a source which roentgenologically cannot be demonstrated. In addition to ulcer and carcinoma, tiny hemorrhagic erosions, small soft benign tumors, and small ulcerations in hypertrophic ulcerative gastritis may bleed; and such hemorrhages, especially in the latter disease, may lead to death. Therefore, as soon as possible, both x-ray examination and gastroscopy should be carried out. It is evident that a small but dangerously bleeding polyp must be removed surgically, while in cases of diffuse hypertrophic ulcerative gastritis, no surgery is indicated. In this connection, it may be mentioned that all workers who compared roentgenologic and gastroscopic findings agree that x-ray examination is not able to diagnose chronic gastritis, except some very rare cases of severe verrucose hypertrophic inflammation. This form was found only 3 times in 450 cases of chronic gastritis.

Gastroscopy becomes still more important if operation in the beginning of the gross hemorrhage is being considered. When a patient before bleeding has been known to have a definite x-ray niche then gastroscopy may seem to be superfluous. That is not so. A short time ago, I observed a patient with acute hemorrhage and marked duodenal fleck. Gastroscopy revealed that a small hemorrhagic erosion of the lesser curvature was profusely bleeding. The bleeding would not have been stopped by the resection of the ulcer. If the source is not known before, operation becomes more or less a gamble. It is well known how

6. *Tuberculous Ulcerations.*—It is well known that gastric tuberculosis is so rare that it has to be considered as almost a curiosity. No gastroscopic reports exist. However, at autopsy, tuberculous tumors of the pylorus and multiple small tuberculous ulcers, usually in the greater curvature of the antrum, have been observed. It should be possible to diagnose these forms correctly, because tubercles, small gray nodules, will be seen at the edge of either lesion. Whether the tumoral form can be differentiated from carcinoma, syphilis, etc., is of no importance in this discussion. It seems unlikely that one would mistake small tuberculous ulcerations for true gastric ulcer, although perhaps their differentiation from gastritic ulcerations might not be easy.

7. *Carcinomatous Ulcer.*—The differentiation between benign and malignant gastric ulcer, especially in small lesions of the lesser curvature, is of the greatest importance for the surgeon. In this differentiation, gastroscopy is superior to the inspection of the gross specimen and is



Fig. 6.—Carcinomatous ulcer. The ulcer is seen at 9 o'clock. Its left border is sharp, but the right one blends with the surroundings. At the right side of the field irregular nodes. At that time clinically still benign ulcer was assumed. Resection two months later proved correctness of gastroscopic diagnosis.

equaled only by the microscopic examination. This statement puzzles the physician who is not the gastroscopist and especially the surgeon and pathologist. Repeatedly the expert gastroscopist makes the diagnosis of a very small ulcerlike carcinoma; the surgeon excises it, inspects it, and considers it benign. The pathologist, well experienced in this condition, makes no macroscopic diagnosis; the microscopic section then proves the correctness of the gastroscopic diagnosis. This superiority of gastroscopy is effected by the presence of circulating blood during the examination. The circulating blood renders the picture plastic and brings out the various colors. The essential gastroscopic difference, as stated before, between a benign and a malignant ulcer is that the edge of the benign ulcer is entirely sharp; whereas, the malignant ulcer at least partly blends with the surroundings (Fig. 6). The color of the floor may be whitish in both the benign and the malignant ulcers; on the other hand, it is sometimes, though rarely, dirty



3. *Erosions of Chronic Atrophic Gastritis*.—Such erosions are rare. They are seen in a thin greenish gray mucosa, are gray of color, and disappear in a few days.

4. *Ulcerations of Chronic Hypertrophic Gastritis*.—Usually this differential diagnosis is easy, but in some cases it may be very difficult, and a final decision may be reached only by repeated examination. These ulcerations are yellow and are not so shallow as those of the other types of gastritis. They are multiple, lying in velvety, swollen, often nodular and irregular mucous membranes (Fig. 5). They are much more frequent in the body of the stomach than in the antrum, where they are found only exceptionally. If patients suffering from this severe disease have frequent gastroscopic examinations, it will be observed that the ulcerations heal rapidly (within three to four days), but that ulcerations in another location appear. I never have observed this ulcerative form of chronic hypertrophic gastritis in connection with chronic gastric ulcer. Great diagnostic difficulties may arise when a single ulceration is seen in a markedly hypertrophic, inflamed area. Fortunately, these cases are very rare. In two such cases observed over a long period of time, I first saw an area of hypertrophic gastritis. Later an ulceration in this area was seen which did not develop into chronic gastric ulcer but which disappeared completely after a few days. Under my observation, I have never seen a true gastric ulcer develop from hypertrophic gastritis. If the described doubtful picture has been found, the patient should have another gastroscopy one week later. If the ulcer then has completely disappeared, the diagnosis of chronic hypertrophic gastritis can safely be made.

5. *Syphilitic Ulcerations*.—I have not seen untreated syphilis of the stomach and have observed but two treated cases showing scar formation. Since the end of the war, syphilis has been eliminated by adequate propaganda and treatment so thoroughly in Germany that in the past ten years it has been almost impossible to show a primary chancre as well as the tertiary lesions to students of medicine. Therefore, I have to refer to Moutier's description. He saw a large elliptical ulcer in a tumor-like swollen surrounding. The floor of the ulcer was quite yellow, baconlike. The picture in Montier's textbook represents a typical gumma which when seen in this form could not be mistaken for any other kind of ulceration. I had the occasion to observe one case (by courtesy of Leon Schiff, General Hospital, Cincinnati) which had been treated only for a short period. Stiff nodular infiltration of the posterior wall was seen. Differentiation from infiltrating carcinoma without ulceration would have been impossible without the knowledge of the serologic findings. Schiff told me that previously through the gastroscope he had seen superficial ulcerations which had disappeared following antisyphilitic treatment.

tion that all nodes, elevations, crests, and pouches seen around stomas in postoperative stomachs are artefacts caused by the operation. Every invagination, every prominent suture line the surgeon carries out remains unaltered through the lifetime of the patient.

The stomachs of patients who regain health after operation for gastric ulcer are peculiar as far as the stoma is concerned. I described, in 1923, that in such cases the stoma of a gastroenterostomy has a pylorus-like, rhythmical action. It opens and closes with stellar formation in a distinct rhythm. This rhythm is different from that of the pylorus, a fact demonstrable when pylorus and gastroenterostomy are observed in the same visual field (Fig. 7). Although this type of stoma does not protect against recurrent ulcer, it does protect almost invariably against gastritis of the postoperative stomach. It seems that gastroenterostomies of the distal part of the stomach are more apt to develop the rhythmical function than those of the upper two-thirds. Direction



Fig. 7.—Gastroenterostomy with normal rhythm. The cavity seen is the antrum, bounded by the "angulus." In the background the open pylorus. At 2 o'clock the gastroenterostomy closing with a stellar formation.

and size of the incision may also play a rôle. This is still a wide field for surgical research. In the last few years, I have observed stomas of resected stomachs that also have shown the same rhythmical action.

Four anatomic diseases of the stomach operated on for ulcer may be observed: (1) recurrent, marginal, and jejunal ulcers; (2) chronic gastritis and jejunitis; (3) silk sutures hanging into the cavity of the stoma; and (4) obstruction of the stoma. A fifth disease, carcinoma of the stoma, apparently does not occur after gastric operations for chronic ulcer, and, therefore, a discussion of it will be omitted in this chapter.

1. *Recurrent, Marginal, and Jejunal Ulcer.*—Recurrent ulcer of the postoperative stomach does not differ gastroscopically from the original ulcer. In one instance, there were six definite, though shallow, ulcers seen in the lesser curvature.

The marginal ulcer gives an unmistakable picture. It is always almost completely white. Gastroscopically its diagnosis is easier than in

gray or brownish even in benign ulcers; but the gradual passing to the surrounding orange red color proves malignancy with certainty. Another important sign of malignancy is the irregularity of the floor. The nodules formed by the lobuli of the pancreas described above must not be mistaken for malignant nodules; more characteristic are ridgelike excreescences never occurring in benign ulcers. I observed one case in which an ulcer roentgenologically appeared probably to be benign and which gastroscopically even had a sharp edge; but from its floor projected a narrow gray ridge; therefore, carcinoma was diagnosed, and the diagnosis was proved to be correct after resection and microscopic examination. Stiffness of the mucosa surrounding an ulcer also is a sign of malignancy, but its recognition is very difficult even to the expert. Sometimes it is so marked that it cannot be mistaken for the more soft hypertrophic gastritic changes around a benign ulcer. Formation of nodes around the ulcer is a very characteristic sign of malignancy. These nodes are big and irregular and can easily be differentiated from the equal small nodules of hypertrophic gastritis.

The gastroscopic picture of the great majority of ulcerated carcinomas is very characteristic. The floor is dirty brown, or violet, or gray of color, often covered by necrotic pieces. The edge is irregularly ragged, blending with the surroundings. A wall surrounds the ulcer which often has an irregular nodular appearance; its color usually is dark red, in contrast to the pale pinkish anemic mucosa. In other cases, the dark red ulcer is surrounded by brilliant white necrotic mucosa.

Ulcerations seen in high elevated papillomatous or polypoid tumors or in lymphoblastoma cannot be mistaken for benign ulcer.

#### FINDINGS IN THE STOMACH AFTER OPERATION ON GASTRODUODENAL ULCER

Although gastroenterostomy and gastric resection in gastroduodenal ulcer result in different physiologic conditions, the same gastroscopic findings have been observed in both types of postoperative stomach; therefore, a separate description is superfluous.

The gastroenterostomy stoma usually is well seen gastroscopically. In rare cases, it remains hidden from view in a blind spot on the posterior wall. Stomas of resection are easily seen. In an astonishingly great number of cases of resected stomachs, the flexible Wolf-Schindler gastroscope enters the intestine. Its interior can then be well observed. It is characterized by the circular parallel jejunal pliae and the Kerkring folds. These are also sometimes seen through the stoma of a gastroenterostomy with the gastroscope still entirely in the stomach. The color of the intestine is a little bit browner than that of the stomach. The edge of the stoma rarely is smooth and round. Often an elevated wall is seen containing nodules and even polyplike formations. These, however, are pseudopolyps, for after repeatedly comparing operative procedures and subsequent gastroscopic pictures, one gets the convic-

tered the jejunum to a depth of ten centimeters. There the mucosa was entirely normal. In withdrawing the instrument, the second loop of the coil was observed, and peristaltic waves of the jejunum were seen. The mucosa at this point was normal. By withdrawing the instrument still further, the jejunum close to the stoma was observed. The proximal three jejunal plicae and the edge of the stoma presented a great number of small, dirty, grayish ulcerations. The ridges of these plicae looked moth-eaten. The gastric mucosa of this patient presented all signs of severe hypertrophic gastritis but without any ulcerations. Treatment, continued over months, diminished the subjective complaints of the patient considerably, but the objective findings remained unaltered. It should be emphasized that this picture was found only once in 117 cases of postoperative stomachs.

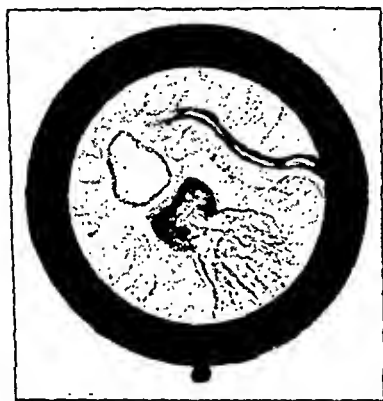


Fig. 9.—Gastroenterostomy. Marginal ulcer. Silk suture. The black hole is the gastroenterostomy, evacuating intestinal juice into the stomach. Above, the white large ulcer and the black silk suture.

3. *Silk Sutures*.—Surrounding an artificial stoma, silk sutures are often found, covered by transparent mucosa. They are seen as black hook-shaped lines and are innocent foreign bodies not causing any subjective symptoms. Occasionally one of these sutures cuts through the mucosa and then is seen as black thread, hanging freely into the lumen. The parts of the suture emerging from the mucosa are yellowish. This type of foreign body is not innocuous. The silk suture, by means of the rhythmical peristalsis of the stomach, is rubbed along the mucosa; an area of very marked, usually erosive, superficial gastritis can be seen. In one instance, I saw such a long suture at the posterior margin of a gastroenterostomy, while a large marginal ulcer had developed at the anterior margin (Fig. 9). It was impossible to prove whether the silk suture had caused the ulcer. Both ulcer and silk suture were found in the resected specimen. Microscopically typical foreign body giant cells were present. Probably all cases in which silk sutures hang free in the gastric cavity need reoperation.

the gross specimen, because of the brilliant colors while the blood still is circulating. In one instance, a marginal ulcer was suspected by x-ray examination. Gastroscoopically it was easy to find this crater, but three additional ulcers were seen. This proves that small ulcers of the stoma are better seen by gastroscopy than by x-ray.

The jejunal ulcer offers greater difficulties. Sometimes its location may be so low down in the jejunum that it cannot be seen, but in other cases it is easy to observe the interior of the jejunum, and then the diagnosis can be made without difficulty. In a case of resection, I followed such a jejunal ulcer by thirteen gastroscopies (Fig. 8). With medical treatment, it finally healed completely.

2. *Chronic Gastritis and Jejunitis*.—All gastroscopists agree that chronic gastritis is by far the most frequent disease of the postoperative stomach. All kinds of changes are seen: superficial edema, patchy reddening, purulent secretion, hypertrophic swelling, inflammatory



Fig. 8.—Jejunal ulcer. The edge of the stoma (case of resection) and the jejunal plicae are well seen. Purulent secretion, the right edge of the ulcer.

erosions, and even atrophic areas. All observers agree that this complicated type of chronic gastritis is the worst one and cannot be cured unless it is possible to undo the gastroenterostomy. In such a case, I saw rapid healing of the inflamed mucosa.

Since rhythmical action of the artificial stoma protects against this gastritis, it must be assumed that the uncontrolled reflux of intestinal juice constitutes the decisive etiologic factor. It cannot be decided whether the chemical or the bacteriologic qualities of the intestinal juice are of greater importance.

Henning found that chronic jejunitis frequently is combined with chronic gastritis. Reddening and purulent secretion of the jejunum occur, but they are rare. Chronic inflammation of the stomach usually ends exactly at the margin of the stoma. In a single case which was examined gastroscopically four times, we saw the rare picture of ulcerative jejunitis. The patient had undergone a resection because of duodenal ulcer. He developed gastric pain. The gastroscope easily en-

Gastric ulcers are sometimes missed by roentgenoscopy, found by gastroscopy, and vice versa. The final healing stage of ulcer can be determined only by the gastroscope; this is true also as regards the detection of accompanying inflammation and of the differential diagnosis from carcinomatous ulcer.

COMMENT; VALUE OF GASTROSCOPY IN GASTRODUODENAL ULCER  
FOR THE SURGEON

1. Gastroscopy reveals gastric ulcers not demonstrable with other methods.

2. The success of medical treatment, complete epithelization, can be determined only by gastroscopy.

3. Gastroscopy usually permits the differentiation between benign and malignant ulcer of the lesser curvature.

4. Early diagnosis of very small carcinomatous ulcers and their successful surgical treatment would more often become possible if each patient, in whom a crater of the lesser curvature had been found roentgenologically, were over thirty-five years of age.

5. The extent of inflammation accompanying gastroduodenal ulcer can be determined only gastroscopically. This may be of decisive influence upon the indication for operation. Probably the surgeon would not operate on an inflamed area because he would be afraid of the gastritis that might develop later in the postoperative stomach.

6. The source of gross hemorrhage may be determined gastroscopically. The respective findings either facilitate surgery or prevent it.

7. Recurrent marginal or jejunal ulcers of the postoperative stomach often can best be seen by gastroscopy. If after repeated gastroscopies they have been shown to be refractive to medical treatment, surgical treatment may be considered.

8. Gastroscopy permits the physician to observe whether or not an artificial stoma is working in the normal rhythmical way.

9. Gastroscopy alone permits the diagnosis of the most common disease of the postoperative stomach, chronic gastritis, and jejunitis.

10. Gastroscopy reveals the presence of free silk sutures in the postoperative stomach. These constitute a definite indication for reoperation. Also, rarer complications in the postoperative stomach, such as obstruction of the intestine by adhesions, occasionally may be diagnosed gastroscopically.

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4. *Obstruction of the Stoma.*—Modern surgical technique makes the artificial stoma large enough to avoid obstruction. I never have seen a case with stoma too narrow for the regular passage of food. Gastroscopy at times permits unusual diagnoses. In a patient suffering from recurrent epigastric pains after gastroenterostomy, I saw the stoma easily; it was contracting rhythmically, pushing with each contraction brilliant white material into the stomach. This observation was not an entirely new one for me. In 1922, I had observed the same phenomenon, but then the ejected material had been dirty, gray, irregular necrotic particles, a picture which immediately permitted the diagnosis of a necrotic tumor below the gastroenterostomy, which was confirmed by subsequent operation. In the quoted case, however, the material ejected from the intestine into the stomach was not necrotic tissue, but of brilliant white color resembling the barium often found in the stomach if gastroscopy is carried out too soon after x-ray examination. The patient was questioned and said that three days before (!) he had taken bismuth powder. The unusual diagnosis of obstruction of the intestine beyond the gastroenterostomy was made and was proved correct by operation (S. Strauss). The pathologist (Saphir) found that immediately below the gastroenterostomy the loop of the intestine was pulled upward and fixed on the gastric wall by adhesions. There a large pouch formation of the intestine was found. Evidently the intestine was obstructed by the adhesions; the bismuth powder had remained in the pouch and had been pushed back into the stomach by rhythmical contractions.

#### BRIEF COMPARISON BETWEEN GASTROSCOPY, GASTROPHOTOGRAPHY, AND ROENTGENOLOGIC EXAMINATION

Gastrophotography has been done with the gastrophotor, a small camera which, after introduction into the stomach, permits the exposure of eight films. The results, even with improved optical system, are not satisfactory for two reasons: (1) it is impossible to know which area of the complicated gastric surface is seen on the developed and magnified film; (2) the most sensitive films do not satisfactorily differentiate yellow and red colors so important in gastroscopy, especially in the diagnosis of ulcer. This latter disadvantage is best shown by making photographs through a rigid gastroscope. The brilliant yellow surface of a gastric ulcer appears on the film exactly as gray as the surrounding orange red mucosa does. The presence of the ulcer can only be judged by the shadow cast by an overhanging undermined edge. Therefore, gastrophotography is considered valueless.

Roentgenologic examination is, on the whole, of greater value than gastroscopy in gastroduodenal ulcer, in contrast to carcinoma and chronic gastritis. Ulcers of the duodenum and of the pyloric canal cannot be seen by gastroscopy but are easily demonstrated by x-ray examination if modern relief compression technique with localized exposures is used.

tension of some part of the stomach or duodenum, and not as a rule to actual "soreness" of the ulcer. The ulcer, however, may act as a source of reflex irritation which may set up spasm and consequent indigestion; in this sense it is a more or less direct cause of symptoms. The argument briefly outlined above has been discussed at length elsewhere.<sup>2</sup>

It becomes clear then that there are two somewhat distinct problems in connection with the treatment of peptic ulcer, (1) the relief of symptoms and (2) the healing of the ulcer; these do not necessarily go hand in hand, and each has its separate surgical implications.

*Indications for surgery from the standpoint of elimination of the ulcer.*—As long as a peptic ulcer remains unhealed, it constitutes a hazard for the patient. One can never tell when perforation or serious bleeding will occur; one cannot be sure that scarring, adhesions, and obstruction will not develop. With unhealed ulcer of the *stomach*, there is the added risk, by no means insignificant, of the development of cancer. Theoretically, then, one might conclude that peptic ulcers should be promptly excised if at all resistant to medical measures, and, were the operation simple and safe and the results permanent, no one would dispute this position. But there are many well-known difficulties and disadvantages. Even in the best hands there is a sizeable mortality from gastric operations; with the ulcer safely out other symptoms may supervene; and recurrences after operation are of course frequent. This last and very serious difficulty is evidently due to the fact that some people tend to form ulcers repeatedly and the excision of any single lesion fails to reach the root of the trouble. It is clear then that no formula of procedure can be derived and the decision to advise operation will always include many intangibles, such as the patient's reaction to illness, his economic status, his age, the availability of supreme surgical talent, and many others.

*Indications for surgery from the standpoint of relieving symptoms.*—The tendency in recent years has been to veto the idea of operation in cases of peptic ulcer unless perforation, obstruction, serious bleeding, or other complication has supervened. The point at issue is whether surgical interference is ever indicated purely for the relief of "indigestion" in patients with simple peptic ulcer. We believe that it often is indicated for the following reasons: If the immediate cause of symptoms is an abnormal state of spasm or tension of gastroduodenal muscle, and if over a reasonable period of time diet and other medical measures have failed to give relief, then one may be entirely justified in attempting to break up these abnormal states of motility by means of operation. The difficulty is to know just what to do, and the very multiplicity of procedures which have been advocated shows that surgeons have discovered no really rational basis for their manipulations. Whether they cut or suture here or there, relief is obtained in a certain proportion



## THE INDICATIONS FOR OPERATION IN CASES OF UNCOMPLICATED PEPTIC ULCER\*

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IN THIS symposium our part concerns itself with the indications for operation in the case of uncomplicated peptic ulcer—that is to say, ulcer without pyloric obstruction, perforation, or notable bleeding. It is a difficult question, and in the individual instance important arguments both pro and con can usually be assembled; hence there can never be any dogmatic answer or simple formula of procedure.

The ground can perhaps best be cleared by presenting briefly our own philosophy of the symptoms of peptic ulcer, already exposed in other articles.<sup>1, 2</sup> First of all it must be emphasized that the exact mechanism of the production of discomfort in people with ulcer is not at all clear. Two main views are held. The first and the most widely advocated maintains that the open ulcer, irritated by acid, is the direct cause of pain, just as a sore on one's hand is painful. The second regards the ulcer as one incident in a syndrome featured by indigestion and (as a rule) a profuse secretion of highly acid gastric juice; the symptoms are thought to be due, not to acid irritation of the ulcer, but to spasm, or at least an abnormal state of tension of the gastroduodenal muscle. It is this latter view which we believe to be correct for the following reasons:

1. Ulcer may develop to the point of perforation with no symptoms of any sort.
2. So-called "ulcer symptoms"—indigestion—may continue after the ulcer is healed.
3. Symptoms may continue after the ulcer is excised.
4. "Ulcer symptoms" may exist in a patient in whom no ulcer has ever been demonstrated.
5. Nonulcerative lesions, such as a polyp, may be associated with so-called "ulcer symptoms."
6. "Ulcer symptoms" can best be reproduced in man by mechanical procedures, such as inflation of the duodenum by balloons.
7. Relief of "ulcer symptoms" by soda can be achieved by doses of alkali too small to neutralize the gastric contents.
8. Relief of symptoms can at times be produced by nonalkaline substances.

All this, we believe, supports the view that the "indigestion" of patients with noncomplicated ulcer is due to abnormal states of spasm or

tension of some part of the stomach or duodenum, and not as a rule to actual "soreness" of the ulcer. The ulcer, however, may act as a source of reflex irritation which may set up spasm and consequent indigestion; in this sense it is a more or less direct cause of symptoms. The argument briefly outlined above has been discussed at length elsewhere.<sup>2</sup>

It becomes clear then that there are two somewhat distinct problems in connection with the treatment of peptic ulcer, (1) the relief of symptoms and (2) the healing of the ulcer; these do not necessarily go hand in hand, and each has its separate surgical implications.

*Indications for surgery from the standpoint of elimination of the ulcer.*—As long as a peptic ulcer remains unhealed, it constitutes a hazard for the patient. One can never tell when perforation or serious bleeding will occur; one cannot be sure that scarring, adhesions, and obstruction will not develop. With unhealed ulcer of the *stomach*, there is the added risk, by no means insignificant, of the development of cancer. Theoretically, then, one might conclude that peptic ulcers should be promptly excised if at all resistant to medical measures, and, were the operation simple and safe and the results permanent, no one would dispute this position. But there are many well-known difficulties and disadvantages. Even in the best hands there is a sizeable mortality from gastric operations; with the ulcer safely out other symptoms may supervene; and recurrences after operation are of course frequent. This last and very serious difficulty is evidently due to the fact that some people tend to form ulcers repeatedly and the excision of any single lesion fails to reach the root of the trouble. It is clear then that no formula of procedure can be derived and the decision to advise operation will always include many intangibles, such as the patient's reaction to illness, his economic status, his age, the availability of supreme surgical talent, and many others.

*Indications for surgery from the standpoint of relieving symptoms.*—The tendency in recent years has been to veto the idea of operation in cases of peptic ulcer unless perforation, obstruction, serious bleeding, or other complication has supervened. The point at issue is whether surgical interference is ever indicated purely for the relief of "indigestion" in patients with simple peptic ulcer. We believe that it often is indicated for the following reasons: If the immediate cause of symptoms is an abnormal state of spasm or tension of gastroduodenal muscle, and if over a reasonable period of time diet and other medical measures have failed to give relief, then one may be entirely justified in attempting to break up these abnormal states of motility by means of operation. The difficulty is to know just what to do, and the very multiplicity of procedures which have been advocated shows that surgeons have discovered no really rational basis for their manipulations. Whether they cut or suture here or there, relief is obtained in a certain proportion

of cases, whereas in others, things are no better or even worse. It seems reasonable that operations planned primarily to relieve symptoms of indigestion should include not only an excision of the ulcer, since it may be the trigger zone for indigestion reflexes, but also a plastic procedure which yields a wide outlet in the pyloric region. From a physiologic standpoint, this would seem to offer the best chance of averting "ulcer indigestion," although the degree of benefit to be achieved in the individual case can never be correctly predicted.

In conclusion, we feel strongly that both surgeons and internists have been thinking in narrow terms with too much emphasis on the ulcer itself; symptoms too often are blamed directly on it, therapy centers wholly on its healing or elimination; and not enough stress is laid on the fact that tendency to ulcer formation, indigestion, and a high gastric acidity are as a rule the common *results* of some underlying diathesis or disorder. Elimination of the ulcer alone may no more cure the entire disease than treatment of nephritic retinitis will cure the sick kidney; they are both the effects of a common cause.

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# ACUTE MASSIVE HEMORRHAGE FROM THE UPPER GASTRO- INTESTINAL TRACT

WITH SPECIAL REFERENCE TO PEPTIC ULCER

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THE rapid loss of a large quantity of blood from any source is always alarming. Few conditions with which the physician has to deal create more uncertainty than the patient who, with little or no warning, feels faint and then vomits a basin full of blood. Such individuals may have little or no nausea but a desire to defecate and find that a large liquid stool is black or even bright red. Frequently fainting actually takes place and the family may discover the unconscious victim on the bathroom floor.

When the physician arrives, he finds the patient in some degree of shock. There is obvious pallor, sweating, restlessness, and a rapid pulse. Usually these individuals are recognized as potential casualties and are referred to the nearest hospital for treatment. Immediately the question arises concerning the source of the hemorrhage. One must bear in mind that even with the ulcerated vessel on the duodenal side of the pylorus most of the blood may be vomited. Thus in a previous study<sup>1</sup> of 371 bleeding duodenal ulcers occurring in a ten-year period at the Massachusetts General Hospital, we found 22.6 per cent had hematemesis only, 38.3 per cent had melena only, and 39.1 per cent had both hematemesis and melena. One naturally thinks of the most frequent source of such massive hemorrhage from the upper gastrointestinal tract, i.e., duodenal ulcer. There are, however, several other lesions of this region that bleed profusely and that produce the same acute picture. These are gastric ulcer, gastric carcinoma, gastrojejunal ulcer, esophageal varices, leiomyosarcoma, and hypertrophic gastritis. A brief discussion of these lesions over the same ten-year period, 1923 to 1932, occurring in the Massachusetts General Hospital will be set forth. However, special reference to the management of peptic ulcer associated with massive bleeding will be our chief consideration.

During the decade from which this study was made, there were 72,447 admissions to the wards of the Massachusetts General Hospital. Two hundred and thirty-one or 1 out of every 313 patients, were brought in for acute massive bleeding from the upper gastrointestinal tract. These are represented as follows:

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Received for publication, April 8, 1937.

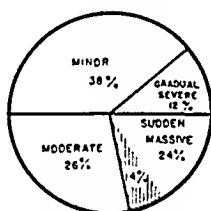
Duodenal ulcer	94	Esophageal varices	37
Gastric carcinoma	45	Gastrojejunal ulcer	8
Gastric ulcer	42	Leiomyosarcoma	3
Hypertrophic gastritis	2		

The incidence of massive hemorrhage in all these lesions admitted during the same period are represented in Table 1. Fifty-one of the to-

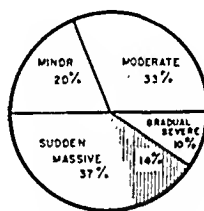
TABLE I  
SUDDEN MASSIVE HEMORRHAGE—1923 TO 1932 INCLUSIVE

	TOTAL CASES	SUDDEN MASSIVE CASES	DEATH FROM HEMORRHAGE
Duodenal ulcer	1002	94	13
Gastric ulcer	434	42	6
Gastric carcinoma	615	45	13
Gastrojejunal ulcer	35	8	2
Esophageal varices	219	37	14
Leiomyosarcoma	4	3	1
Gastritis	22	2	0

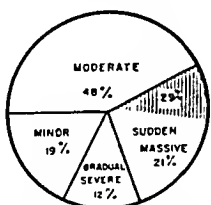
BLEEDING CASES—1923—1932 INCLUSIVE



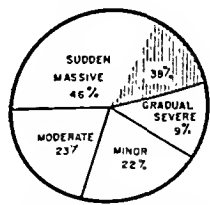
DUODENAL ULCER—390 CASES



GASTRIC ULCER—12 CASES



GASTRIC CARCINOMA—214 CASES



ESOPHAGEAL VARICES—81 CASES

SHADED AREA—PERCENTAGE OF SUDDEN MASSIVE CASES DYING OF HEMORRHAGE

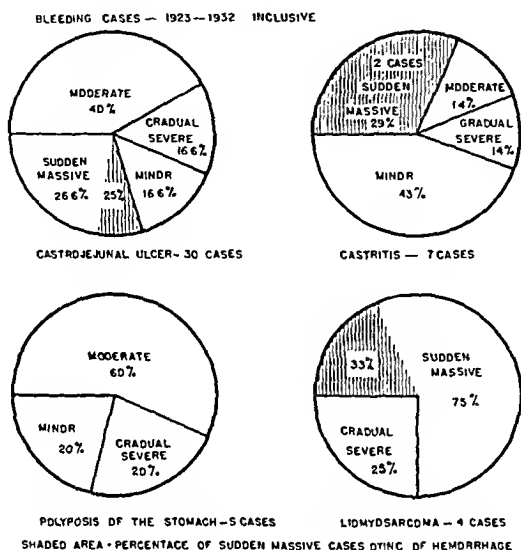
Graph I

tal acute hemorrhage cases, or 22 per cent, died of hemorrhage while in the hospital. The various factors contributing to the differential diagnosis and the treatment of those from peptic ulcer will be considered.

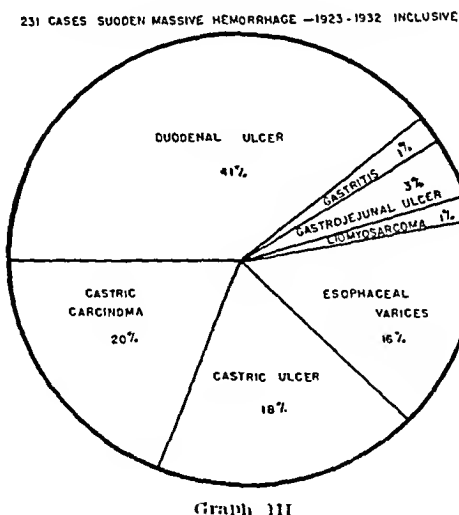
#### DUODENAL ULCER

This diagnosis was made, 1,002 times on ward patients during the interval under discussion. Of these, 390 had gross bleeding detectable while under observation. Ninety-four bled profusely and actively in sufficient quantities to produce shock and acute anemia. In addition, 48 more bled sufficiently to finally attain the minimum level, or below

it, to be classed as severe bleeders, although slowly enough to create no emergency. All of the cases in the acute massive group and in the gradual severe group were found to have red blood counts below three million and hemoglobin below 70 per cent. Thirteen of these patients bled to death.



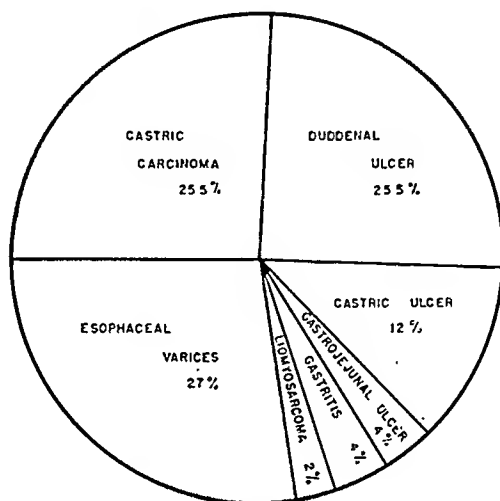
Graph II



In a previous communication, Allen and Benedict<sup>2</sup> analyzed all of the common factors in a similar series of cases over a twenty-year period in an effort to find what could be determined regarding the cause of continued bleeding and death in these patients. It has been frequently

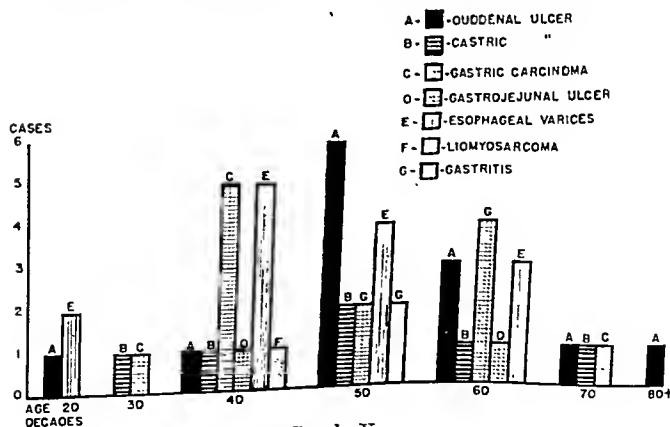
stated that, although such individuals may almost bleed to death, they rarely do. Our analysis showed that the age of the patient had more bearing on the question of spontaneous cessation of hemorrhage than any other factor. In 90 patients who bled acutely and massively before the age of fifty years, only 4 died. In 42 patients who were over fifty years of age, 14, or exactly one-third, died of hemorrhage. Al-

51 DEATHS FROM SUDDEN MASSIVE HEMORRHAGE—1923-1932 INCLUSIVE



Graph 1V

AGE DISTRIBUTION—51 DEATHS FROM SUDDEN MASSIVE HEMORRHAGE—1923-1932 INCLUSIVE



Graph V

though it is well known that women are less likely to have duodenal ulcer than men in a ratio of about 1 to 4, those women who do have duodenal ulcer are just as prone to bleed profusely, but in our small series they were much more likely to have a spontaneous remission than men of the same age. Chronicity of the ulcer, habits, occupation, premen-

vious bleeding, etc., seemed to play no rôle in the question of recovery. Nine out of 20 fatal cases died from their first period of massive hemorrhage. Also, it was found that if operation was delayed for a week or more in a patient continuing to bleed either constantly or with repeated episodes every day or two, no patient was saved by surgery regardless of what was done.

Faced with these facts, we must consider what can be offered these patients; first, in the acute phase; second, in the quiescent state. In the early hours of acute massive hemorrhage from duodenal ulcer, we may well say that if the patient is under fifty years of age and has elastic vessels, conservative measures are indicated, because it is unlikely that we can hope to operate upon them and ligate their bleeding vessels

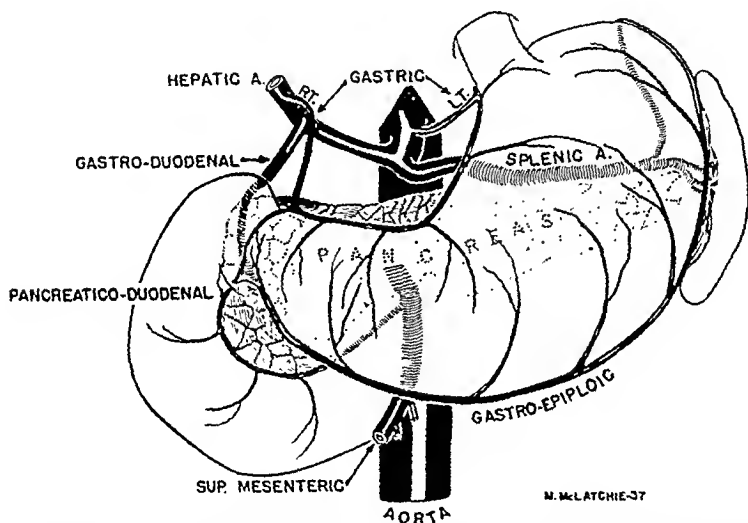


Fig. 1.—Schematic drawing indicating the course of the gastroduodenal artery behind the first portion of the duodenum. Note the direct communications between this vessel and the gastropiploic and the pancreaticoduodenal arteries, all three vessels arising from different sources.

with a mortality of less than 5 per cent. In the older age group, however, we can justly use Finsterer's<sup>3, 4</sup> much quoted forty-eight-hour time limit to advantage. Certainly in the good risks we should be able to definitely improve a mortality rate of 33½ per cent which occurred in those treated conservatively.

When one considers the type of ulcer that produces this picture and its relation to the blood vessels in this region, it is easy to understand that as these vessels become eroded, the inelasticity of the vessel wall in later life will materially influence effective clot formation. The deep penetration of the posterior wall ulcer into pancreatic tissue, at a point where the gastroduodenal artery transveres it, increases not only the risk of continued bleeding but makes any operative procedure one of



major consideration. As shown in Fig. 1, we see that this vessel anastomoses in such a way as to make it necessary to ligate it between its three different sources and the ulcer area. One can hardly expect to open

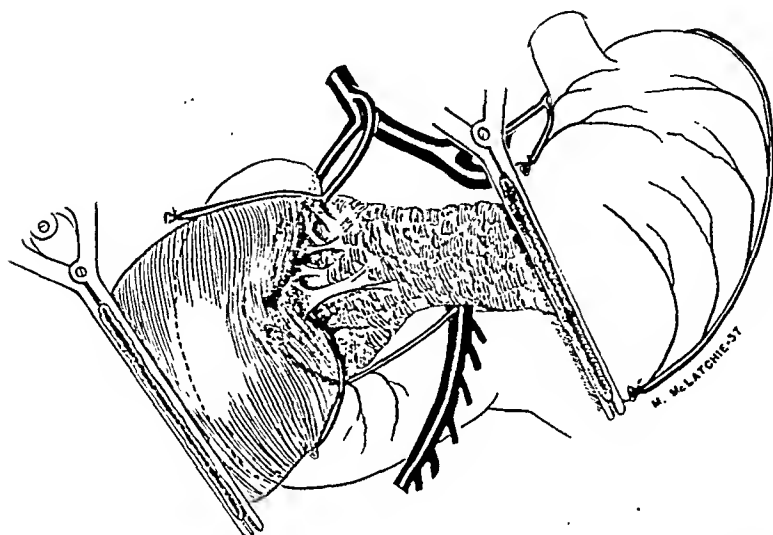


Fig. 2.—Schematic drawing illustrating the method of approach to the bleeding area in the posterior wall duodenal ulcer with erosion into the pancreas. The stomach has been transected and the distal portion elevated.

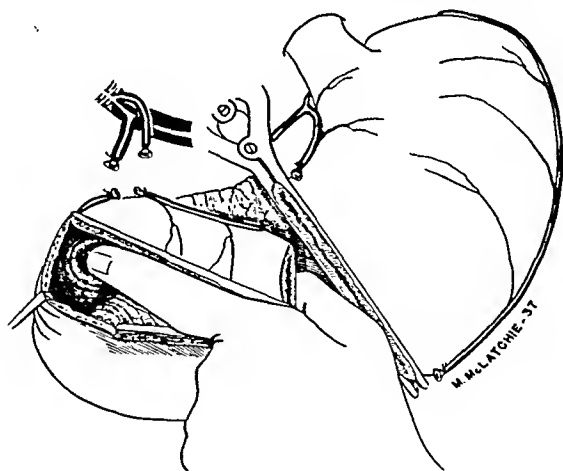


Fig. 3.—Schematic drawing illustrating control of the bleeding vessel by compression with the index finger of the left hand. The distal segment of the stomach has been widely opened down the anterior surface through the pylorus. Note the opportunity of visualizing the papilla of Vater.

the anterior wall of the duodenum and successfully place ligatures in this friable ulcer bed, nor can one safely pass stitch ligatures in such a way as to occlude the vessels in healthy tissue from within. This method

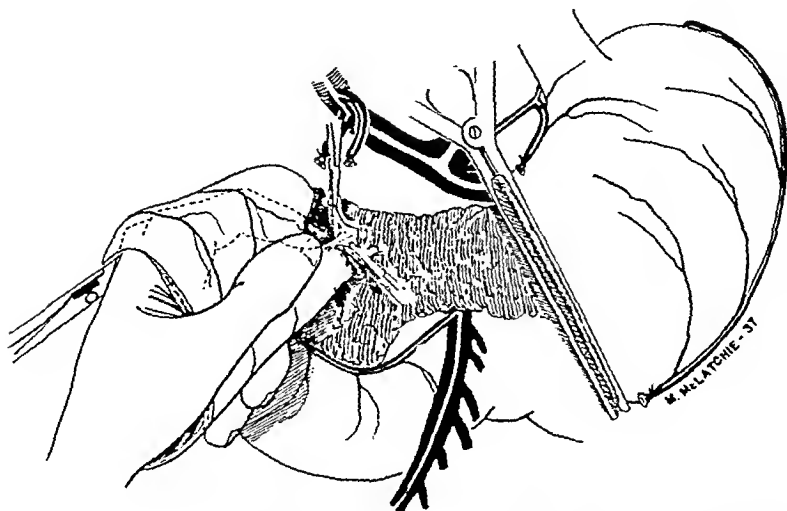


Fig. 4.—Schematic representation of ligating all vessels leading into the inflamed area. The ulcer has entirely eroded through the duodenal wall, into pancreatic tissue. It is broken into from behind and no attempt is made to remove or cauterize the ulcerated portion of the pancreas.

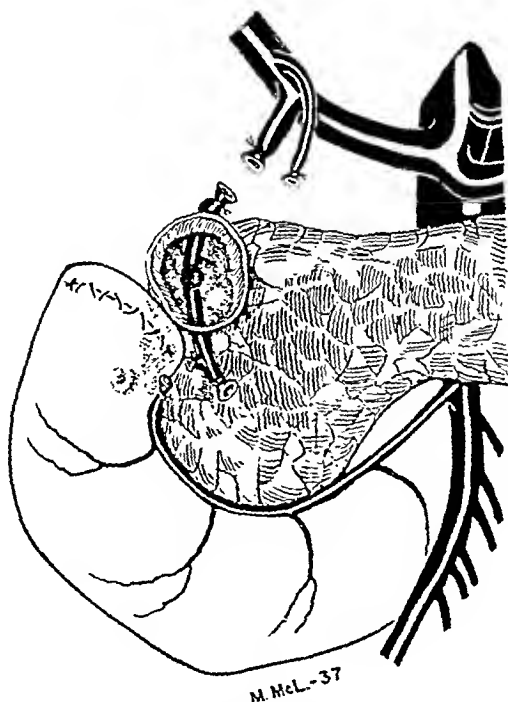


Fig. 5.—Schematic drawing of the ulcer and eroded vessel with the duodenum freed on the distal margin and turned in well above the papilla of Vater. The eroded pancreas can be covered with a tab of omentum. Stab wound drainage to the sub-hepatic space of Morrison can be instituted if one fears leakage from an injured or eroded accessory pancreatic duct.

has succeeded in isolated instances but more often has met with failure either from loss of blood on the table or from further necrosis and secondary bleeding.

Finsterer<sup>3-5</sup> advocates direct tamponade in some extensive ulcerations into the pancreas with a secondary resection after the patient has recovered from the effects of blood loss. When he can, with reasonable safety, complete his operative procedure in one stage, even in acute bleeding, he does so; and one would judge from his writings that he is carrying out radical procedures in the majority of such cases. In a

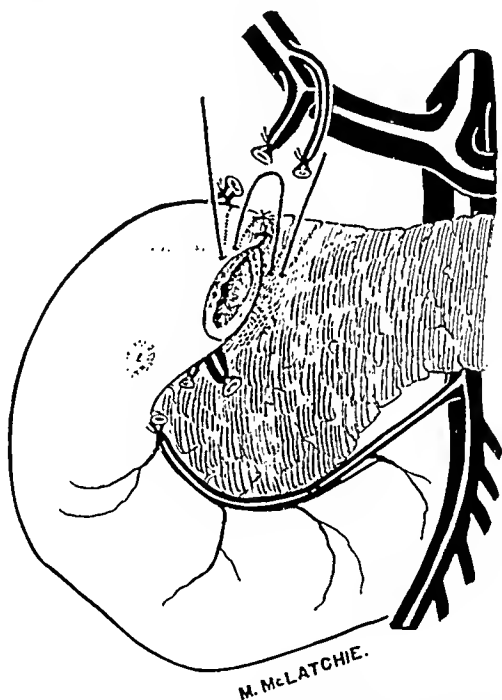


Fig. 6.—If the ulceration is low on the duodenum, and the location of the papilla of Vater is such that closure of the duodenum cannot be safely accomplished as illustrated in Fig. 5, one can leave the posterior margin of the duodenum attached and suture the anterior edge to the pancreatic capsule. It is important to approximate the serous coat of the duodenum to the pancreas. This can be reinforced by omentum. This method has the advantage of allowing any pancreatic secretion that may exude from the ulcer bed to drain into the duodenum.

large group of actively bleeding ulcer patients, he has successfully ligated the bleeding vessels and resected the distal two-thirds of the stomach with a very low mortality, 5 per cent, or less, if the operation was undertaken within forty-eight hours of the onset of hemorrhage. He has not refused to operate on those patients who have been referred to him late; i.e., after a week or more of continued or repeated bursts of profuse bleeding. In this late group, his mortality has been 30 per cent. He apparently feels that by excluding the extensive, deeply penetrating ulcer on the posterior wall of the duodenum, by transection of the

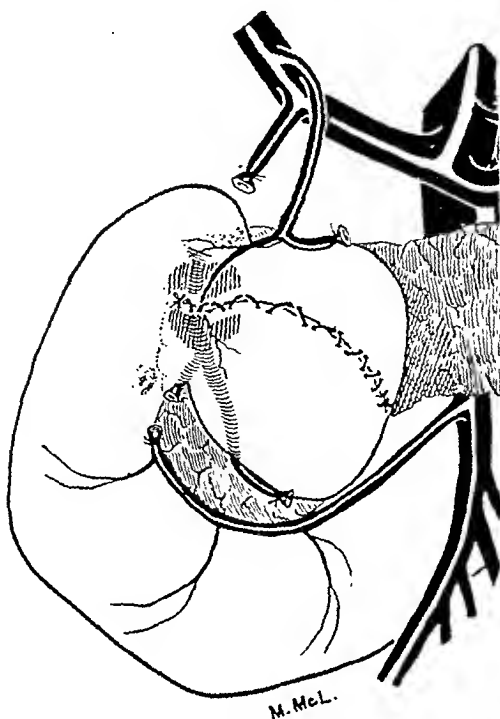


Fig. 7.—Schematic representation of a method of closing a small portion of the distal segment of the stomach over the ulcer bed after the vessels have been ligated under vision. One may facilitate the closure of this region by removing the mucous membrane as suggested by Bancroft.<sup>19</sup>

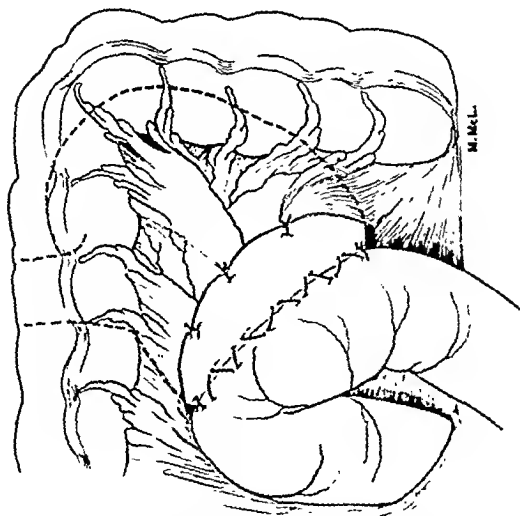


Fig. 8.—The high posterior Polya anastomosis should be made with a short loop, the proximal jejunum placed to the lesser curvature. It should be arranged to enhance direct drainage from the stomach into the distal limb of the jejunum.

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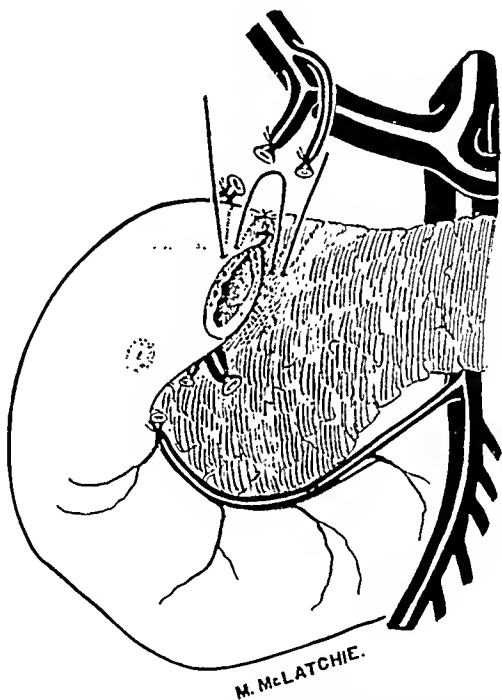


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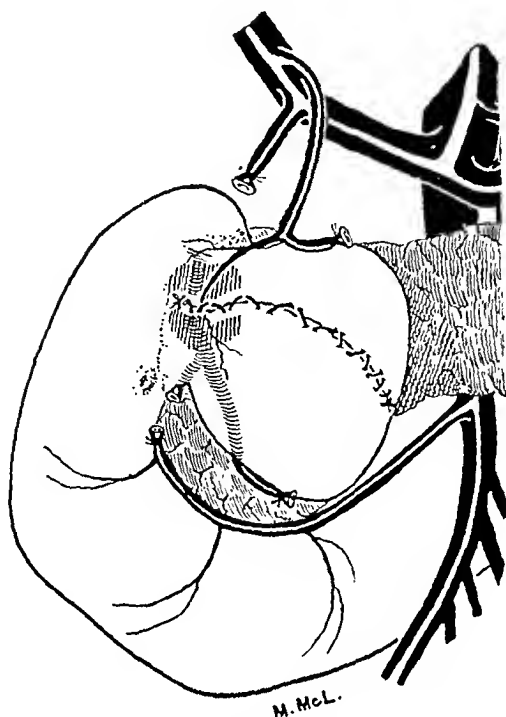


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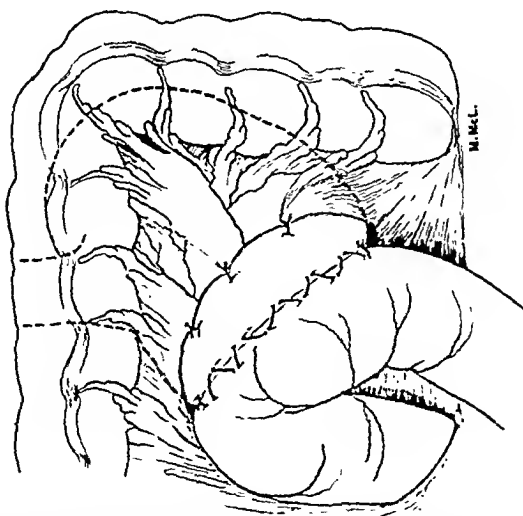


Fig. 8.—The high posterior Polya anastomosis should be made with a short loop, the proximal jejunum placed to the lesser curvature. It should be arranged to enhance direct drainage from the stomach into the distal limb of the jejunum.

duodenum proximal to the ulcer, or by transection of the antrum two fingerbreadths from the pylorus, and then removing the distal two-thirds of the remaining stomach, his end-results are nearly, if not entirely, as good as when the actual ulcer area in the duodenum is included in the resection. He calls this operation "resection for exclusion." We are of the opinion that in doing this operation the radicals leading into the ulcer bed are ligated.

Many surgeons have had the experience of failure in gastroenterostomy for massive hemorrhage in duodenal ulcer. These patients continue to bleed and finally succumb to anemia because the eroded vessel leading into the ulcer bed is still open. In those instances where bleeding has



Fig. 9.—Ulcer on the posterior wall of the duodenum. Patient is supine with right side up. Thick barium coats the stomach, pyloric valve, and duodenum and the gas bubble in the stomach fills the antrum, pyloric valve, and duodenum, thus allowing double contrast examination.

stopped and the patients have recovered for the time being following gastroenterostomy, we believe that usually the bleeding would have subsided spontaneously on conservative treatment. We have offered<sup>2</sup> a method of control of the bleeding vessel by direct exposure while the dissection and ligation of the main arteries leading into the area is carried out (Figs. 2 through 8). This is a logical procedure and if practiced early in the episode of acute hemorrhage, i.e., as soon as the patient has recovered from the initial shock, will be met with success. The occasion for its use arises infrequently but if considered carefully with known duodenal ulcer, bleeding acutely, if such a patient falls into

the group beyond the age of fifty years, where death from hemorrhage occurs once in three such cases, a certain number of these patients can be reseeded. Trout<sup>6</sup> approves of this procedure, and Ochsner,<sup>7</sup> Sowles,<sup>8</sup> and others besides myself have successfully carried out this operation.

In the quiescent or interval stage of posterior wall duodenal ulcer, particularly after one or more episodes of massive bleeding, one is confronted with the problem of proper treatment. If the patient is young and responds well to a dietary regime, we may justly feel that radical surgery is meddling. This is particularly true if by Hampton's<sup>9</sup> technique of following these patients by x-ray examination, we find that the crater actually fills in and in so doing nature has not caused an obstruction to gastric contents that must pass this region. Certainly some of these patients manage to get along comfortably and safely for many years. On the other hand, it is well known that this type of ulcer, particularly if it has eroded a large vessel, is unusually resistant to medical measures.<sup>10</sup> Not only are such patients prone to have continued or frequently repeated episodes of discomfort, but they also have recurrences of massive bleeding. This occurs even under conditions that appear to be ideal. We believe that radical surgery offers these individuals a more comfortable life and at the same time eliminates the possibility of a fatal hemorrhage from an eroded vessel later, at a time when there may be sufficient sclerosis in the vessel wall to prevent a spontaneous cessation of bleeding. Prior to 1932 we transected the antrum, turned in the ends, and did a posterior gastroenterostomy in fifteen such patients after the method of Devine. The results were disappointing in that many of the patients continued to have periods of activity in their ulcers, as evidenced from their symptoms, and had recurring bouts of bleeding. Since then, we have resected the distal one-third to two-thirds of the stomach and when possible the ulcer-bearing portion of the duodenum in thirty-eight consecutive posterior wall duodenal ulcers that had bled. All of these patients recovered from the operation and remained well for varying periods of time. Some of them have developed new ulcers, either at the stoma of the posterior Polya anastomosis or on the remaining portion of the lesser curvature of the stomach. In each instance that this new ulcer has developed, it has caused episodes of bleeding. None of these patients, however, have so far died of hemorrhage. Thus we have probably protected most of them from fatal hemorrhage by ligating the large vessels overlying the head of the pancreas, but we have failed to alter not only their ulcer diathesis but their hemorrhagic tendency as well. We are now trying a more radical resection of the stomach hoping that we may, by following more closely the technique of Finsterer, come nearer to his 90 per cent of symptom-free patients. Certainly we must eliminate, if possible, not only the likelihood of fatal hemorrhage in such cases, but while so doing, get a high percentage of permanently relieved patients and a low operative mortality. This must be considered



a surgical lesion although radical or even crude, if you choose, until such time as medicine has mastered the whole question of peptic ulcer. Our experience so far would indicate that the more radical the resection, the less likely a poor end-result. Certainly gastroenterostomy in this group as a whole is unsatisfactory. In the elderly patient with cicatricial obstruction, this conservative procedure is most successful. In the more continuously active ulcer lesions of the posterior wall, penetrating or bleeding cases, we feel that anything short of a two-thirds gastrectomy will give a high percentage of failure. One cannot compare this group with all duodenal ulcers. Doubtless the high ratio of cures twenty years ago following gastroenterostomy was due to the physiologic changes brought about by this operation, the majority of which today are cured by medical measures. Such a large proportion of all ulcer cases are successfully treated conservatively now that when surgery is resorted to for persistent symptoms or massive hemorrhage, we are faced with an entirely different problem. These recalcitrant cases require more than the physiologic changes brought about by pyloroplasty or gastroenterostomy.

#### GASTRIC ULCER

In spite of the fact that a larger percentage of gastric ulcerations are associated with massive hemorrhage, we find coincidentally that the percentage of deaths from hemorrhage is exactly the same as in duodenal ulcer (Table I). The average age of these fatal cases is slightly lower than in duodenal ulcer, but still there is not the marked difference in the age of the patient that we expected to find. One has the advantage then of classifying acute massive bleeding from peptic ulcer on the same basis, whether it be gastric or duodenal, as far as treatment is concerned. The type of operation may be varied in the two lesions and one has a better chance for a two-stage operation in the gastric lesion. The ulcer should be widely exposed and the vessels leading into the eroded one must be ligated in healthy tissue outside the stomach wall. This is usually best accomplished by a free incision into the normal anterior wall of the stomach so that the bleeding vessel can be visualized and compressed during the process of ligating the anastomosing branches. With this accomplished, one can close the opening in the anterior wall and allow the patient to recover from this experience. An operation of election for relief of the persistent ulcer, if such exists, can be carried out to better advantage four to six weeks later. If possible to avoid gastroenterostomy at the time of the emergency procedure, the secondary operation is less restricted as to choice. One may be able to free the ulcer and resect it entirely at the first operation. This is an excellent method and sometimes the most feasible one to insure ligation of the vessels involved in the hemorrhage. This is likely to be the case if the ulcer has penetrated the pancreas. When it can be done or must be done as the procedure of choice, then a superimposed gastroenterostomy may

prove sufficient to eliminate a secondary operation of election. One cannot help feeling less radical about extensive resections in bleeding gastric ulcer, since gastrojejunal ulcer is so much less prone to follow posterior gastroenterostomy in this group than in those done for relief of duodenal ulcerations. Benedict<sup>11</sup> found no instance of stomal ulcer in posterior gastroenterostomy done for gastric ulcer in our hospital.

#### GASTROJEJUNAL ULCER

When acute massive hemorrhage is associated with a stomal ulcer, we must be prepared to consider the possibility of a fatal outcome. The inflammatory process may involve and erode a large vessel such as the gastroepiploic or the colic arch. This offers a very difficult operative procedure because it is usually necessary to take down the old anastomosis in order to find the bleeding vessel. We believe, however, if this is attempted in the early days of bleeding that success will follow in more than 75 per cent of such procedures; since in our 8 cases, 2 succumbed to hemorrhage on a conservative regime. One is again reminded of the care that should be used in placing the opening in the mesentery of the transverse colon through which the anastomosis between the jejunum and the stomach is made, as far away from the main vessels as possible. This point is usually stressed on the basis of keeping the anastomosis as far away from the colon as possible so that a jejunal ulcer may be less likely to become further complicated by a gastrojejunoecolic fistula.<sup>12</sup> It is now generally conceded that gastrojejunal ulceration is unlikely to respond to conservative measures, and certainly there can be little argument against surgery if such lesions have produced active massive bleeding.

#### CARCINOMA OF THE STOMACH

With the comparative frequency of massive hemorrhage in gastric carcinoma, it may seem odd that no such case has been subjected to emergency surgery under the impression that we were dealing with benign ulceration. As a matter of fact, the diagnosis is frequently obvious or so strongly suspected that this error has not been made. These patients are nearly always cachectic; there has usually been a very short period of gastric disturbance; weight loss has been striking; and often a mass is felt. Distant metastases, particularly in the pelvis, are common. When acute massive hemorrhage occurs in such patients, one has little initiative for carrying out anything but palliative measures. If the patient recovers from the bleeding, then the question of resection must be considered. Peritoneoscopy has been found of great value in determining the operability in gastric cancer. The 20 per cent of five-year cures in this disease (Parsons<sup>13</sup>) makes it worth while to continue radical surgery in any case without liver involvement or distant metastases. In eleven consecutive total gastrectomies for adenocarcinoma in

our hospital, six have survived the operation. One is apparently free of recurrence three and one-half years after operation. We should be constantly on the lookout for the linitis plastica type as here one could have every hope of a cure.

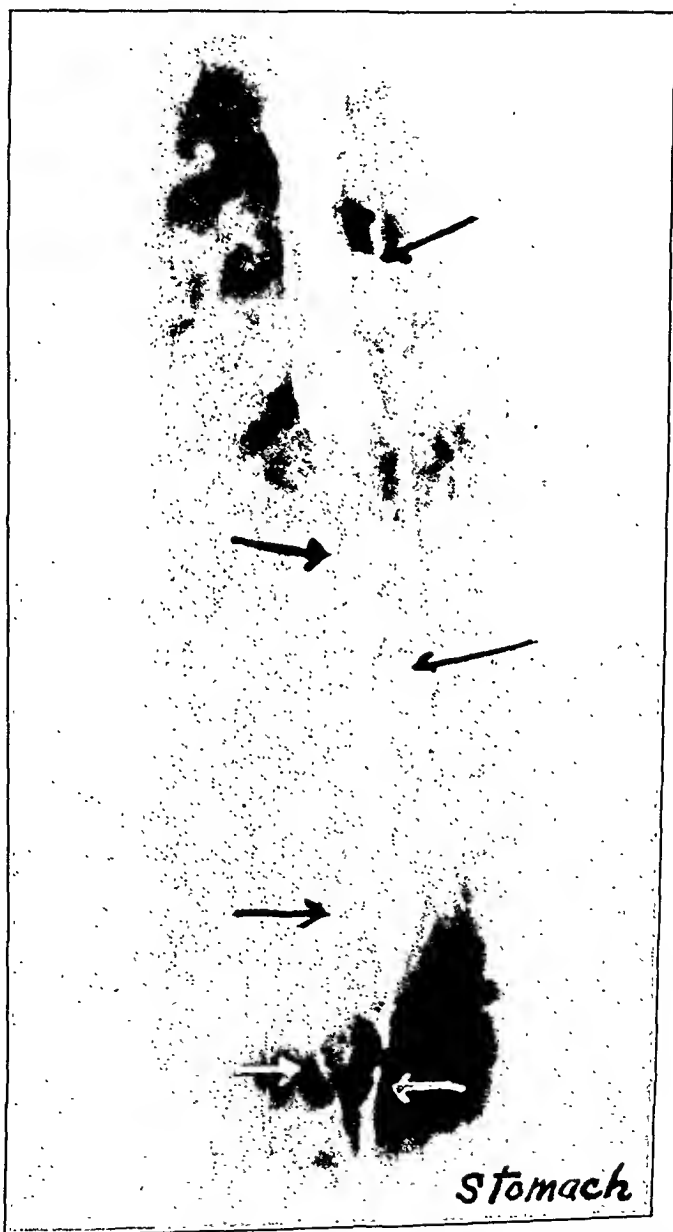


Fig. 10.—Typical picture of varices in the esophagus. Left anterior oblique view: respiration suspended at quiet breathing after the ingestion of thick barium mixture.

## ESOPHAGEAL VARICES

Death from acute massive hemorrhage in varices of the esophagus may occur in a patient with no previous hospital record. In the majority of such cases, however, there are neither previous studies that have pointed to cirrhosis of the liver or thrombosis of the splenic vein. When the diagnosis is in doubt and the evidence points to a remediable hemorrhage from peptic ulcer, one is justified in carrying out x-ray examination of the esophagus by Seitz's<sup>14, 20</sup> method, even in the presence of brisk bleeding. It is interesting to note that since this method of examination has come into practice in our hospital we find the diagnosis of cirrhosis of the liver and esophageal varices made twice as often as it was in the ten-year period immediately prior to 1932.

## LEIOMYOSARCOMA

A very small series in this group, but the tendency for massive hemorrhage is striking. The prognosis with operation is so good that should the diagnosis be made, we should consider surgery in the early hours of bleeding. These lesions have a characteristic x-ray appearance. A large sessile tumor that is smooth in outline with a small deep crater is found. This leads to the serosa, and the bleeding comes from an erosion of a good-sized vessel on the outer surface of the stomach, often on the lesser curvature.

## HYPERTROPHIC GASTRITIS

It seems difficult on first impression to account for fatal hemorrhage from gastritis alone, but in two instances in this series, no large open vessel could be found at postmortem. There was in one of these fatal cases a very large area involving approximately two-thirds of the mucosa and that had been almost entirely cast off, forming what resembled a huge, very shallow ulceration. This patient had consumed large quantities of some strong alcoholic beverage shortly before entry. She vomited an enormous amount of blood and died within forty-eight hours of acute anemia. One may feel that this was in the nature of a chemical erosion, and perhaps it should be so considered. The other death seemed to be based on a true hypertrophic gastritis with enormously enlarged rugae, and at autopsy there was no single large eroded vessel. The massive hemorrhage had apparently taken place from the engorged mucosa extending over practically the whole interior of the stomach.

During the past four years, since a better x-ray technique for gastritis has been developed and with the advent of gastroscopy<sup>15</sup> as a frequent means of study, the diagnosis of hypertrophic gastritis has been made ten times as frequently in our hospital as it was in the ten-year period covered in this study.

## POLYPOSIS

Bleeding must occur to some extent at some time or other in nearly all of these cases, although only five of the cases in this group showed gross bleeding while under observation. It was somewhat of a surprise that none of them in this decade had sudden massive hemorrhage and none died of acute anemia. When one sees the size of the blood vessel in the stalk of some of these polyps, it is not hard to visualize that erosion with massive and even fatal hemorrhage is a possibility. One such patient died in our hospital in 1933.<sup>21</sup>

## COMMENTS

Details as to the conservative management of acute massive bleeding have not been considered a part of this discussion. We feel, however, that some questionable points along this line may be briefly discussed to advantage.

*Blood transfusion* has been criticized as a method of treatment in the early stages on the basis of interfering with nature's efforts to bring about clot formation in the open vessel. We have all seen patients bleed again after a transfusion and frequently have felt that by hastening the elevation of blood pressure and increasing the volume of blood we may have brought about a fresh burst of bleeding. On the other hand, we have seen patients die from the lack of a transfusion and in no instance have we seen transfusion responsible for fatal hemorrhage. We do feel that continuous drip transfusion as advocated by Marriott and Kerwick<sup>16</sup> can be carried too far. It is easy to tell when this blood is lost as rapidly as it is put in, and under such circumstances, it should not be relied upon as a method of cure. Gordon-Taylor,<sup>17</sup> one of the early advocates of this method, has now changed his ideas concerning its efficacy. He now believes that Finsterer's principles are the most logical and practices the forty-eight-hour rule in any case that continues to bleed. All of us are in accord with the importance of blood replacement. We should have a considerable amount of compatible blood on hand if operation in the acute stage is to be undertaken. We feel that donors should be lined up and 500 c.c. of citrated blood kept in the refrigerator for instant use in every case of acute massive hemorrhage. We further believe that this should be withheld in the early stages of hemorrhage until the systolic blood pressure has fallen to 70 mm. One should not delay beyond this point, however, and citrated blood given slowly at this time will not elevate the blood pressure rapidly or restore the blood volume so abruptly as to blow out any clot that may be forming at the site of the open vessel. If such a patient under observation spontaneously ceases to bleed, then even after several days, the prepared blood can be given to hasten the normal restoration of blood elements.

*Sedation* of a patient actively bleeding has been a questionable point. Bulmer<sup>18</sup> believes that too much morphia may be the cause of a higher

mortality, in recent years, in this group of patients. He admits that better transportation facilities may play a rôle in that more such patients are delivered alive to the hospital. Finsterer<sup>5</sup> warns against too much morphia in these depleted patients prior to operation. We should consider this phase of the problem carefully, as we are aware that the restless stage of shock may be harmful, and doubtless there is a proper middle course.

We are inclined to feel that an inlying Levine tube may be worthy of consideration in massive bleeding from the stomach or duodenum. The situation is not exactly similar to the elimination of clots in the urinary bladder, but more or less the same principle is involved. At any rate, this tube allows the aspiration of gastric and salivary secretion which may hinder clot formation. Also, it offers an opportunity to identify fresh episodes of bleeding prior to the point of nausea and vomiting or fall in blood pressure. Without doubt it minimizes the peristaltic activity in this region by keeping the stomach empty. Also, it eliminates vomiting which in itself may dislodge a life-saving thrombus in the open vessel.

In the active stage, fluids should be given by hypodermoclysis rather than intravenously<sup>4</sup> or by proctoclysis. The latter method increases peristalsis which in itself mitigates against physiologic rest. Lavages of ice water and adrenalin are of little value, and both would appear to interfere with nature's efforts. The whole basis of treatment should be rest, quiet, and comfort. Under these circumstances, a spontaneous cessation may be expected in the majority of cases.

*Anesthesia.*—Much has been said about local anesthesia and splanchnic block as a method of choice if operation is undertaken during acute bleeding. This would seem to work more satisfactorily in the hands of some surgeons than others. If the operation is done within the first forty-eight hours, the patient should have no more likelihood of respiratory complications than a carefully prepared patient for gastrectomy in the elective stage. We believe that an unsuccessful local anesthetic, accompanied by nausea or a restless patient during the operation, will do more harm than an expertly given inhalation anesthetic. We prefer a combination of novocaine block and gas-oxygen-ether, both being started in the operating room at approximately the same time. If the inhalation gases are given in a closed type of machine, excellent control can be maintained and the patient always lightly anesthetized. Whether novocaine only, general anesthesia alone, or a combination of the two are used, it is important to eliminate vomiting during the operation. A properly functioning Levine tube to which suction is applied aids greatly in this respect. We believe that basal anesthetics in their usual doses are very dangerous in these depleted patients and for this reason should not be used at all, since it is so difficult to properly gauge the

dose under these circumstances. Careful administration of small doses of morphia one-eighth to one-quarter of a grain is safe and helpful.

*The operation* if undertaken in the acute stage must be carefully planned. It is a poor one to attempt in the middle of the night with an inadequate staff. After all, one has a reasonable amount of time for preparation if the surgeon and internist are willing to work together on these problems. Plenty of compatible blood should be available and the definite steps of the whole procedure thought out beforehand. If this is done, the mortality should be low, even though the operation is of a radical nature. If we should elect to subject all patients with acute massive hemorrhage from peptic ulcer, regardless of age, to operation in the early days of bleeding, we could indeed expect a low mortality. Taking only such cases beyond the age of fifty years, we still feel that these individuals should be carefully considered on the basis of comparative mortality with early surgery properly carried out, versus expectant treatment.

#### SUMMARY AND CONCLUSIONS

1. The relative frequency and causes of cases of acute massive hematemesis admitted to a large general hospital in an urban community have been considered.

2. Death from acute bleeding in the upper gastrointestinal tract occurred in 51 out of 231 such cases.

3. Peptic ulcer accounted for 67 per cent of these massive hemorrhages and 41 per cent of the deaths.

4. The age of the patient with peptic ulcer is the most important factor in the prognosis. Duodenal ulcer rarely causes fatal bleeding under the age of fifty years, while beyond this age the mortality is 33.33 per cent.

5. Operation is urged in the better risk patients in the older age group in the acute stage of bleeding. Delay should not be extended beyond forty-eight hours. The bleeding vessels should be ligated.

6. Peptic ulcer associated with massive hematemesis should be considered a surgical lesion as an elective procedure, regardless of the age of the patient, in those who have spontaneously recovered from an episode of bleeding.

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## PEPTIC ULCER: ITS SURGICAL TREATMENT BY CONSERVATIVE MEASURES

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*(From the Mayo Clinic)*

THE ideal of surgical treatment of any chronic nonmalignant disease is to bring about relief of symptoms and prevent recurrence of the disease, and to achieve these aims by the simplest and safest possible method. The trend of surgery will always be toward such a standard of perfection, and although this trend in respect to simplicity and safety of operation may be carried to such an extreme as to lead to ineffective treatment, persistence in such efforts in many fields of surgery has profoundly changed, and at times even eliminated, formerly accepted methods of treatment. This trend has been evident in the management of varicose veins, prostatic obstruction, inguinal hernia, and cancer of the uterine cervix, and it has contributed much toward the satisfactory management of such conditions by the use of methods and principles which are more simple, even though they may require measured judgment and even more exacting technical skill in their execution than the more radical procedures. In peptic ulcer, attempts to control the disease by conservative measures have had a thorough trial, and an appraisal of the value of these methods is always necessary in any consideration of the treatment of this disease.

The general principles of the treatment of peptic ulcer have changed considerably within a relatively short period. It has become increasingly apparent that the medical management of peptic ulcer is on a more satisfactory basis than ever before and that, as a result of this, relatively fewer patients with the disease require surgical treatment. This improvement in medical treatment has evolved to a large extent from a wider recognition of the fact that satisfactory healing of the lesion is most likely to be effected when a patient thoroughly understands the circumstances under which symptoms are likely to manifest themselves, and adjusts his habits of living so as to eliminate those more common factors which he has found have to do with initiating or aggravating the symptoms. In addition, there is now a better understanding of the administration of alkalies and of the use of buffer substances and those preparations which inhibit gastric secretion. The suggestion recently made that a deficiency of vitamin C may be a factor in preventing healing of the lesion and, particularly, may at

least be a contributing cause to gastroduodenal hemorrhage either with or without ulcer promises to add to the efficiency of medical treatment.

The first step, then, in the treatment of peptic ulcer is the establishment of a conservative regimen based on those general and specific measures which have proved to be valuable; such management maintained over a sufficient length of time will then control the disease and its symptoms in a large percentage of cases. In those cases in which such measures adequately carried out fail to accomplish this control and symptoms persist to a degree to justify surgery, the principles of surgical management require as careful consideration as do those of medical management.

The so-called conservative operations which are employed in the treatment of peptic ulcer may be divided into the indirect and the direct, in respect to whether or not the lesion is removed. The indirect operations, therefore, attain their purpose entirely by modifying gastroduodenal function enough to enable the ulcer to heal, remain healed, and also to prevent recurrence of the disease. It is true, therefore, that the value of the indirect operation is directly proportional to the permanency of its effect in controlling hyperactivity of gastric function, chiefly the secretory and motor mechanism. For this reason such procedures as interruption of the vagus nerve, which may have encouraging immediate effects, may ultimately fail to prevent reestablishment of hyperacidity and even introduce undesirable physiologic disturbances associated with new symptoms. Whether other procedures designed to deal with the acid factor, such as fundusectomy, advocated by Connell, can be developed to maintain a continuous control of the acid mechanism must be determined.

#### INDIRECT OPERATIONS

*Jejunostomy.*—Of the indirect operations, jejunostomy may be mentioned first because from a theoretical standpoint it is the ideal method of bringing about complete rest for the stomach and duodenum. From a practical standpoint, however, the operation is rarely indicated, principally because it does not modify gastric function, as any operation for ulcer must do, and whatever good effect the jejunostomy does have must terminate when the jejunostomy tube is removed; in other words, the maintenance of any treatment of a disease of such chronicity and tendency to recurrence must be possible.

*Operations on the Pylorus.*—The many procedures which have been devised to bring about ablation of the pyloric muscle have been based on the belief that pylorospasm is a factor in both the production and persistence of peptic ulcer and in the production also of the symptoms which are associated with it. Therefore, most of the operations on the pylorus have included either division or resection of the pyloric

muscle, which is designed to eliminate pylorospasm and by this means to prevent gastric stasis and to reduce activity. Usually an added purpose of these reconstruction operations on the outlet of the stomach has been to remove the lesion, but there has been convincing evidence to show, in the case of ulcers of the posterior wall of the duodenum for example, that such lesions heal without recurrence of ulceration following satisfactory reconstruction of the outlet of the stomach. This is particularly true when a small pyloric outlet resulting from hypertrophy or constriction of the muscle has been converted into a large outlet, the continuity of the muscle being permanently interrupted. There are, however, enough recurrences of symptoms and even of ulcer following any of the operations on the outlet of the stomach to make it obvious that this type of operation should be performed only under rather special circumstances. The chief indications exist when other, more effective conservative measures are contraindicated, particularly gastroenterostomy. These contraindications, in turn, are a high-lying stomach, or a previous operation making the performance of gastroenterostomy too difficult, or the presence of high acid values which have shown little modification under medical management. The most favorable group of cases for reconstruction of the pyloric outlet are those of young patients with marked pylorospasm in whom the inflammatory process is confined to the anterior wall of the duodenum.

There seems to be little difference in the results of the various pyloroplasties so long as the general plan originally developed by Finney is adhered to, namely, construction of a large pyloric outlet and permanent ablation of the pyloric muscle. In well-selected cases the results of pyloric reconstruction are apparently satisfactory in about 70 per cent. In those cases in which patients have not obtained what they consider a favorable result, the chief symptom of the majority is a sensation of epigastric distention; in the remainder, a recurrence of definite ulceration actually occurs. An important advantage of the operation, however, is that in the event of recurrent ulceration requiring further surgery the operation may be conducted as a primary procedure.

*Gastroduodenostomy.*—Gastroduodenostomy, as originally suggested by Jaboulay, is occasionally revived with some enthusiasm as a sound surgical treatment for duodenal ulcer. Again, from a theoretical standpoint, it is an operation which has much to commend it, since it is entirely indirect and therefore does not entail the risk which may be associated with removal of the lesion. Gastroduodenostomy can be accomplished with as much safety as any other procedure and provides for a large, added communication between stomach and duodenum. Nevertheless, the operation apparently has rare indications and its use is confined to those circumstances under which no other

procedure can be either easily or satisfactorily performed; under such circumstances it occasionally serves a very useful purpose. Its chief disadvantage, however, is that in cases in which it fails to bring about and maintain healing and control symptoms or in which a recurrence of ulceration takes place necessitating further operation, disconnection of the anastomosis, since it involves the second portion of the duodenum, is technically not easy to accomplish.

*Gastroenterostomy.*—Of the indirect, so-called conservative procedures, gastroenterostomy is the most useful, not only because of the great variety of circumstances under which it may be indicated and the excellent results which follow it in well-selected cases, but also because it is the only operation in which conditions prior to operation can be restored merely by disconnecting the anastomosis. The operation has its greatest application in cases of chronic duodenal ulcer in which there is impairment of motor function and in which the acid values are not unusually high. Since impaired motor function usually occurs late in the development of duodenal ulcer, it is in the most chronic cases that gastroenterostomy is so effective. If the operation could be confined to this group there would be little criticism of it, but the very fact that it did bring about such spectacular results in this group led to its employment in cases in which there was no impairment of motor function and in cases in which symptoms were of short duration. It is probably for this reason that so much criticism of the operation has arisen, because it is in this group that disappointing results are most likely to occur.

The emphasis which has been placed on these disappointing results and the occasional report of a case of jejunal ulcer developing many years after gastroenterostomy have obscured the real facts; namely, that when the indications for gastroenterostomy are understood and carefully observed, the results reported are strikingly similar. Between 80 and 90 per cent of patients have obtained satisfactory results following gastroenterostomy over a period of time much longer than has been reported for radical operations for peptic ulcer. The persistence of symptoms in about 10 to 15 per cent of the cases has been of sufficient degree, however, to justify calling the operation unsatisfactory, although it must be pointed out that these symptoms are less marked than they were before operation and are easier to control. In approximately 3 or 4 per cent of the cases, jejunal ulcers have developed subsequently. In reviewing the disappointing results, including the development of jejunal ulcer, we find that if surgery is required the situation is a fortunate one, because the gastroenterostomy can be readily disconnected, an advantage which is not held by other procedures.

While gastroenterostomy for gastric ulcer is theoretically not the ideal operation, it is a surprising fact that in those cases of gastric

ulcer in which, for some reason, removal of the lesion was not considered feasible and gastroenterostomy alone was done, the operation was followed by healing of the lesion in many cases in which other treatment had previously been of no avail. This fact is clear evidence of the marked influence of gastroenterostomy on healing benign ulcerations of the stomach and, taken in conjunction with the fact that it is almost a rule that if the anastomosis continues to function, any inflammatory process in the duodenum will heal and remain healed, is indicative of the use to which the operation can be put. Further, it has been shown that the prompt regression of gastritis which may be associated with peptic ulcer takes place under the influence of the operation. At the same time, however, one cannot propose gastroenterostomy as the ideal procedure for gastric ulcer because there is no way of absolutely determining at any time, except by microscopic examination, whether or not a gastric ulcer is malignant.

#### EXCISION

A direct operation for peptic ulcer, which might still be classified as a conservative surgical procedure, is excision of the lesion. In rare instances an ulcer may be so situated in the stomach (for example, on the posterior wall some distance from the lesser curvature or even approximating the greater curvature) that excision alone is justifiable. However, if deformity of the lesser curvature results from plastic closure of the defect after excision, this deformity may be responsible for the stasis and recurrence of symptoms and even ulceration which so often followed excision of gastric ulcer alone in the earlier days in the management of the disease. Excision alone, therefore, is rarely indicated for this reason, and also because nothing has been done to maintain any surgical management of the disease in respect to controlling hyperactive gastric function.

Excision of the lesion, therefore, is usually combined with one of the procedures already mentioned, according to the indications in the particular case. Most commonly this is gastroenterostomy, because it is the most effective of the conservative procedures in reducing acidity and in maintaining control of intragastric tension and hypermotility. Occasionally, excision of a gastric ulcer may be combined with reconstruction of the outlet of the stomach, providing the latter can be well accomplished as far as a large opening is concerned. Excision of a duodenal ulcer along with any of the foregoing procedures is theoretically advantageous in the case of the bleeding type of lesion, but results have shown that, in so far as gastroenterostomy is concerned, healing of any lesion in the duodenum may be anticipated; and if hemorrhage does take place after gastroenterostomy for hemorrhagic duodenal ulcer, it is more likely that the hemorrhage is due to causes

other than a recurrence or reactivation of duodenal ulcer unless the anastomosis has become obstructed.

#### COMMENT

As one reviews the many possibilities and combinations of these various conservative procedures and considers the great variability in peptic ulcer in its manifestations in different types of patients, the truth is apparent that the most successful surgical treatment which can be carried out for this disease requires a thorough familiarity with the basis on which patients are selected for operation and the selection of the procedure to be employed. The general principles which have been outlined have been proved over a long period of time to be so useful in the management of the disease, when surgery is clearly indicated, that any surgical method which involves considerably greater risk, unless it can promise absolute freedom from disappointing results (which no operation has, as yet, been able to do), should not be advocated as a routine procedure. The soundest argument for so-called conservative surgical treatment in peptic ulcer is that such methods when intelligently applied yield very satisfactory results, and these conservative measures will probably remain an important part of the surgical treatment of the disease as long as surgery of peptic ulcer is required.

## PYLOROPLASTY AND GASTRODUODENOSTOMY

### A CONSIDERATION OF THE TECHNIQUE AND INDICATIONS FOR THESE TYPES OF OPERATION

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THE first operations to be attempted on the stomach, other than those for the repair of wounds of, or for the removal of foreign bodies from this viscus, were for the relief of obstruction at the pyloric outlet, usually due to a neoplasm. Possibly this statement is not entirely true, inasmuch as the first operations on human beings had been preceded by experimental resections on dogs, in which, of course, there was probably no actual disease. First to attempt such procedure was apparently John Jones, of Philadelphia, who conducted several such experiments in the latter half of the eighteenth century, but who left no present discoverable record of his pioneering work. He was followed, about fifty years later by Merrem, of Giessen, who left an available, though not very detailed, report of stomach resections done on several dogs with discouraging results. Von Winwarter and Gussenbauer, in 1876, following animal experimentation, were encouraged enough to propose the application of this operation of pylorotomy to human beings suffering with pyloric obstruction. This was attempted in 1879 by Péan and in the next year by Rydygier, both unsuccessfully. It remained then for Billroth, in 1881, to do the first successful resection of a tumor at the pylorus in a human being, and in so doing to give to surgery the operation which is yet known by his name, the Billroth I type of pylorotomy and anastomosis. To us, charged in this symposium with the discussion of pyloroplastics and gastroduodenostomies, all of this history is intensely interesting because every one of these early attempts was toward the reestablishment of the normal anatomic relationships, by anastomosing stump of stomach to stump of duodenum—a gastroduodenostomy. Although we do not intend or wish to enter in this article into any controversy on the relative merits of the various types of operations which have since been evolved, it should be said that we feel quite strongly that some form of anatomic restoration of relationships, where possible, is most desirable, and offers better functional results and prognosis than any of the methods involving an anatomic rearrangement. If it were not so, we probably would not have been chosen to write on this particular subject. It is our purpose to discuss and describe as impartially as possible the various operations which embody this principle, their advantages and disadvantages. To do this

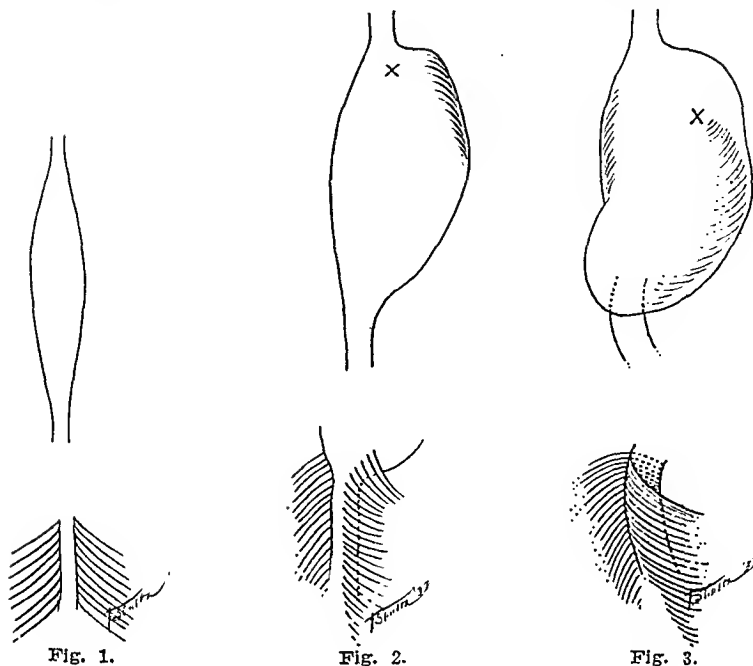


Fig. 1.

Fig. 2.

Fig. 3.

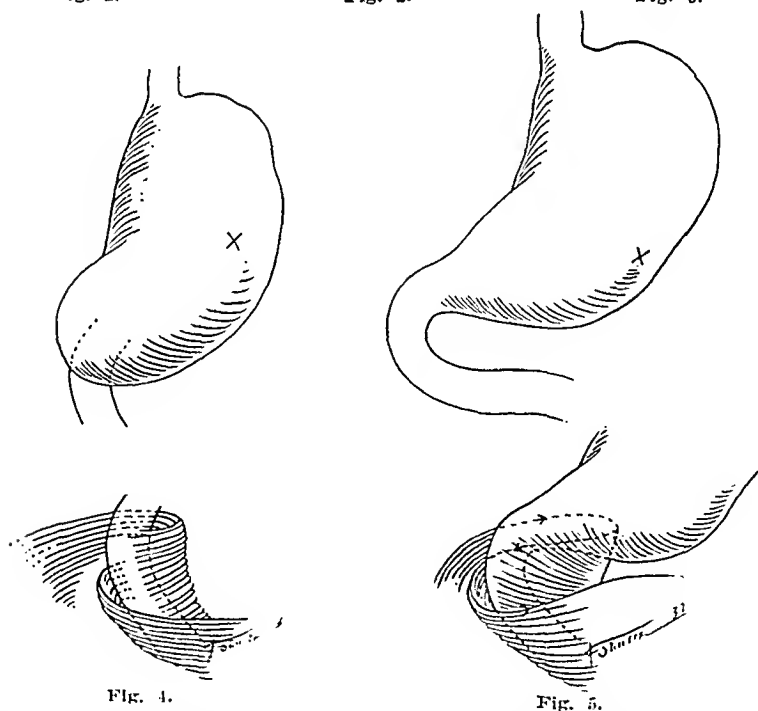


Fig. 4.

Fig. 5.

Figs. 1-5.—Diagrammatic representation of development and rotation of the stomach and duodenum from the primitive enteric tube in the embryo. (Figs. 1-4 viewed from the right side; Fig. 5 viewed from the anterior or ventral surface.)

These show the major enlargement as occurring in the esophageal, or cardiac, end of the stomach, and the primitive anterior and posterior mesogastrum of the pyloric end of the stomach and duodenum, as it is rotated into folds which later, by more or less complete fusion, fix the second and third portions of the duodenum after rotation is complete. It is by separation of these partially fused layers that proper mobilization of the duodenum is made possible and accomplished.



intelligently and clearly we must have an accurate understanding of the anatomy, including embryologic development, and of the physiology of the parts involved; so we shall first review briefly these phases, at the risk of some repetition of and encroachment upon the subject matter of other papers composing this symposium.

The stomach is first recognized in the embryo about the end of the third week, as a dilatation of the enteric tube, which lies vertically in the axis of the body. As this bulge rapidly enlarges, mainly posteriorly—that is, dorsad—it is supported, front and back, between vertical folds of mesogastrium. Primordial buds at the lower end of the bulge, where will eventually be duodenum, give rise, anteriorly, one to the liver and another to the head of the pancreas and common duct, and posteriorly, one to the body and tail of the pancreas. As the stomach pouch enlarges further, the dorsal portion gradually descends and rotates toward the left, while the ventral portion drops backward and slightly toward the right. In this way the superior part of the bulge becomes the cardiac and fundic portion of the stomach, the inferior part the pyloric end and the duodenum. Likewise the posterior portion becomes the greater curvature, the anterior portion the lesser curvature and duodenal cap, the left aspect the anterior surface of the stomach, and the right aspect the posterior surface. This process of rotation and what it entails is most important in surgery involving the duodenum, and should never be left out of account. Upon it depends both the fact that the blood supply of the duodenum enters from the inside of its curve—that is, medially—and that the lateral and posterior fixation of the duodenum, except where it passes under the mesenteric vessels, is accomplished by the fusion of the serosal coat on the right side of its embryonic anterior mesogastrium, with the serosal coat of the dorsal, or posterior, abdominal wall. For this reason, although the second and third portions of the duodenum, in adult life, appear to be retroperitoneal, they strictly speaking are not; and a line of cleavage between the partly fused serosal coats may usually be found, allowing the bowel to be rolled medially about one-half its circumference and somewhat downward, out of its bed in the maneuver spoken of as mobilization. We believe that lack of appreciation and understanding of this fundamental fact accounts for the difficulty in the performance of and poor results following operations involving the pylorus and duodenum in the hands of many surgeons.

There is one other fact that is often lost sight of, which has to do with the anatomy of the stomach, and to which we would here call attention, inasmuch as certain misconceptions seem to be common. The acid-secreting glands are situated in the fundus of the organ, not at the pyloric end. One of the arguments which has been widely employed to favor a resection of the pyloric end of the stomach over some form of plastic operation on the pylorus is that by so doing one removes a large part of the acid-forming area and thereby helps to control any tendency

toward hyperacidity. This is not the case unless an extensive resection is done. On the contrary, the glands in the pyloric portion of the stomach are apparently the same as, or similar to, the Brunner's glands in the duodenum, and their secretion is alkaline. Would it not seem logical, therefore, to preserve them and their secretion so far as possible?

Pylorospasm apparently may be produced by either local direct or distant reflex stimulation, the latter presumably through the vagus nerve. In either event, a vicious circle may be instituted, in which cause and effect of an ulcer near the pylorus seem to become hopelessly entangled. This confusion has led to much argument as to whether ulcer is caused by hyperacidity or whether hyperacidity is a result of ulcer. Into this controversy we do not intend to enter now. One thing seems obvious: that, to remedy the condition, the circle must be broken somewhere, somehow. If, mechanically, the pyloric sphincter is put completely out of commission, then certainly there can be no further spasm. This may be done simply by dividing the muscle entirely, and by so closing the necessary wound that the divided ends remain widely separated and therefore cannot reunite, or, more radically, by complete extirpation of the ring, followed by some type of reestablishment of gastrointestinal continuity. The only alternative to one or other of these procedures is a short-circuiting around this area, at least theoretically throwing it out of the path of active circulation of gastric contents. We qualify this last statement advisedly because it seems quite well established that unless the pylorus has become completely stenosed either by neoplasm or by contraction of scar tissue due to ulcer, material ingested into the stomach will endeavor to follow its normal channel, and to a considerable extent will succeed, even in the presence of a much larger auxiliary but unnatural outlet. This fact may play some part in the occurrence of marginal ulcer following gastrojejunostomy in the presence of a partially patent pylorus, the food-neutralized gastric contents passing to a large extent through the normal channel, thus allowing a high concentration of acid from the adjacent glands to come in contact with the jejunal mucosa at the new stoma. If one adds to this the indisputable fact that the duodenum is accustomed and acclimated to the reception of the acid contents of the stomach as they are expelled through the pylorus, does it not then seem reasonable and natural that normal anatomic relationships should be maintained in our choice of operations, where possible?

There is, however, one entirely independent factor which should modify this choice when we are dealing with an ulcer definitely gastric in origin, namely, the question of malignancy. The occurrence of neoplasms in gastric ulcer has been variously estimated at from 2 to 5 per cent all the way up to almost 70 per cent. Where estimates vary so widely, one person's guess is almost as good as another's. The important consideration is not so much the exact percentage number, but rather the fact

that this can and does occur, and that it may be quite difficult to recognize all cases in this group. Every effort should be made, therefore, to excise the ulcer with a good margin. If this can be accomplished in the course of some type of plastic operation, well and good; if not, then some form of resection which will permit of its complete elimination should be chosen. Due to the relative infrequency of duodenal carcinoma, this consideration need not influence one's choice of operation there.

Fortunately from the standpoint of this possibility of malignant degeneration, duodenal ulcers appear to be much more common than gastric ulcers; again the actual ratio varies considerably as given by different observers, but seems to average at about 3 to 1. This proportion is of interest to us from another angle as well; namely, that the duodenal ulcer lends itself much more readily to some form of pyloroplastic operation than does the gastric. It is also of importance that probably between 80 and 90 per cent of duodenal ulcers are located within an inch or less of the pyloric ring. In the case of the gastric ulcers, while probably 75 per cent or more occur in the pyloric end of the stomach, they may be anywhere up to two or two and a half inches away from the pylorus, a distance which renders the applicability of a pyloroplasty doubtful, but which still permits of a pylorotomy with gastroduodenal anastomosis.

Unfortunately a fairly large proportion of duodenal and pyloric ulcers occur either on the superior margin or posteriorly. Even a larger proportion of gastric ulcers occur on or very near to the lesser curvature. This automatically limits materially the field of utilization for the linear incision types of pyloroplasties—Heineke-Mikulicz, Mayo, and Horsley—but is no contraindication to the employment of the inverted horseshoe incision, sometimes called a gastropyloroduodenostomy—Finney. The latter is very much less limited in its applicability either by distance of the lesion from the pyloric ring or by its position on the circumference of the viscus.

The most potent bar to the employment of a pyloroplasty or gastroduodenostomy (and this is equally true of any type of pyloric resection), is the presence of dense scar tissue and adhesions binding the pyloric end of the stomach and the duodenal cap superiorly to the liver and posteriorly to the common duct, hepatic vessels, and the head of the pancreas. This may render the proper mobilization of the pylorus and duodenum, upon which the success of the operation is dependent, very difficult or utterly impossible. In such instances the use of a short-circuiting operation such as posterior gastroenterostomy becomes necessary. Fortunately also in such cases there is usually a very high grade of pyloric stenosis, which favors the proper functioning of such an anastomosis. To reiterate, it cannot be too strongly emphasized or too frequently stated that the successful result in pyloroplasty or gastro-

duodenostomy is directly dependent upon the complete mobility of the duodenum. Where this cannot be adequately attained, some other form of operation should be chosen.

Coming now to the actual technique of these operations, we will divide them into two natural groups: first, the plastic operations involving the simple division of the pyloric sphincter; and second, the operations involving the exclusion or total removal of the pyloric sphincter. The first group we will call pyloroplasties, the second group gastroduodenostomies.

#### Fredet - Rammstedt

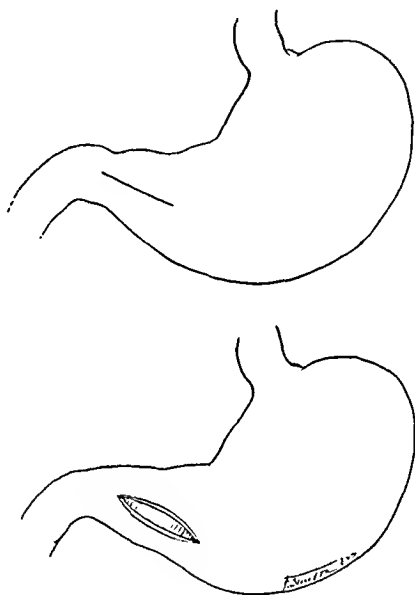


Fig. 6.

#### PYLOROPLASTIES

The first operation to be discussed in this group is one of the more recent contributions and one with a very limited field of application, but in its particular place it is universally accepted as the operation of choice. This is the Fredet-Rammstedt submucous pyloroplasty for congenital pyloric stenosis. First proposed by Fredet in 1907, it followed the principle of the much older Heineke-Mikulicz, in that following the division of the hypertrophied muscle band (but without incising through the mucosal lining, into the lumen of the gut), the linear longitudinal incision was transformed into a transverse wound by suturing the cut muscular and serosal layers, bringing the original ends of the horizontal incision together first to be the midpoint of the new vertical suture line, and continuing from there upward and downward until the defect

that this can and does occur, and that it may be quite difficult to recognize all cases in this group. Every effort should be made, therefore, to excise the ulcer with a good margin. If this can be accomplished in the course of some type of plastic operation, well and good; if not, then some form of resection which will permit of its complete elimination should be chosen. Due to the relative infrequency of duodenal carcinoma, this consideration need not influence one's choice of operation there.

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tion was reported independently less than a year later by Mikulicz. Hence it has become known as the Heineke-Mikulicz pyloroplasty, the pioneer of all plastic operations on the pylorus. The description of the technique as given in excerpts from Frommüller's original report of the first operation done by Heineke is as follows: ". . . A longitudinal incision was made in the anterior wall of the pylorus. . . . The lumen of the pylorus now opened proved to be so narrow as scarcely to admit a large knitting needle. After the longitudinal incision had been considerably enlarged on the stomach side as well as on the pyloric side, one could introduce the finger in either direction. . . . In order to remove the constriction . . . the longitudinal wound of the pylorus was drawn into the transverse direction and thus sutured transversely, in the vertical direction. In this manner the stomach angle of the wound was sewed to the duodenal angle and the anterior wall of the stomach was united to the anterior wall of the duodenum. The sutures were placed close together in a double row." Mikulicz's description of technique differs in no essential way from that just quoted except that he says: "If a fresh, possibly bloody or perforating ulcer is found, one turns his attention to this first." This at least suggests the possibility of the excision or cauterization of an ulcer in the course of such an operation, as well as an enlargement of the constricted pylorus. It also rather accurately suggests the limitations of this type of operation. An ulcer on the anterior surface of stomach or duodenum, if within an inch or less of the pylorus and if not too large, may easily be excised if, instead of a linear longitudinal incision, a long narrow elliptical incision be employed, with one limb of the ellipse encircling each side of the ulcer. If the ulcer is on the superior—that is, lesser curvature—side, or the inferior—greater curvature—side, this type of operation is virtually impossible and is therefore not indicated. If the ulcer is directly posterior, it may be possible, after the linear incision is made and the cut edges retracted, either to cauterize the ulcer from within the gut lumen, or better, to excise its edges and base, being careful not to penetrate the posterior muscular layer completely; and then by undermining the surrounding mucous membrane, bring it together with a running or buttonhole lock stitch of fine catgut, to cover this raw area over the excised base. The wound in the anterior wall is then closed in the original manner at right angles to the line of incision, either by a row of mattress sutures of fine silk, turning in the cut edges, and then reinforced by a second row of Lembert sutures of silk, or if one prefers, by a first row running mattress or Connell stitch of fine catgut, which likewise inverts the edges nicely, reinforced by a second row of interrupted or continuous silk. This may then be covered by a flap of gastrocolic or gastrohepatic omentum, or by a portion of the round ligament of the liver, if desired. Such reinforcement is particularly appropriate if one has been dealing with a perforated ulcer, since the stomach and

was completely closed. Such closure was frequently rendered difficult by the almost cartilaginous consistency of the hypertrophied muscle bundle, and also tended again to encroach somewhat on the lumen of the gut. Hence the modification suggested in 1912 by Rammstedt, which simply omitted all attempt at suturing and left the mucosa bulging through the elliptical defect in the pyloric muscle, has been almost universally adopted. This raw area may or may not be covered over by some fat from either the gastrohepatic or gastrocolic omentum as the operator may choose. The pylorus in an infant is best reached through a short right rectus incision, placed rather near the medial margin of the muscle

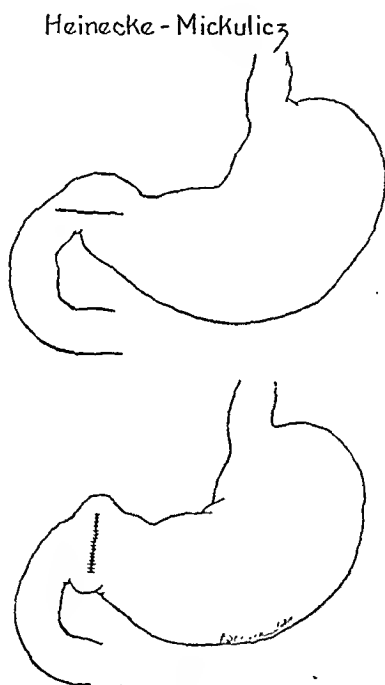


Fig. 7.

and not too high toward its costal insertion, remembering that the liver edge generally reaches from three to five centimeters below this landmark. The pylorus, being usually much more mobile in the infant than in the adult, can often then be delivered out of the wound, and the operation performed outside the abdominal cavity. After closure of the peritoneum with a running suture of fine catgut, the wound is best closed in anatomic layers with interrupted sutures of fine silk, for infant's tissues do not tolerate and absorb catgut very satisfactorily. The results of this operation are as near perfect as one could ask of any operative procedure.

Chronologically, the first plastic operation on the pylorus was reported from Heinecke's Clinic in 1886. Virtually the identical opera-

the underlying principles of the operation. The abdomen is opened by a high right rectus incision, curving the upper end medially along the costal margin, if necessary, to gain proper exposure in cases where the duodenum and pylorus are lying in a high transverse position. Careful examination is then made of the local lesion and its suitability to this type of operation is determined. The superior margin of the duodenum just beyond the pylorus, and occasionally including it, is freed from any adhesions and from the supporting ligament running to the undersurface of the liver. This is done by a small incision along the duodenal margin, followed by peeling out the duodenum bluntly with the fingers, aided at times with gauze, or rarely by sharp dissection.

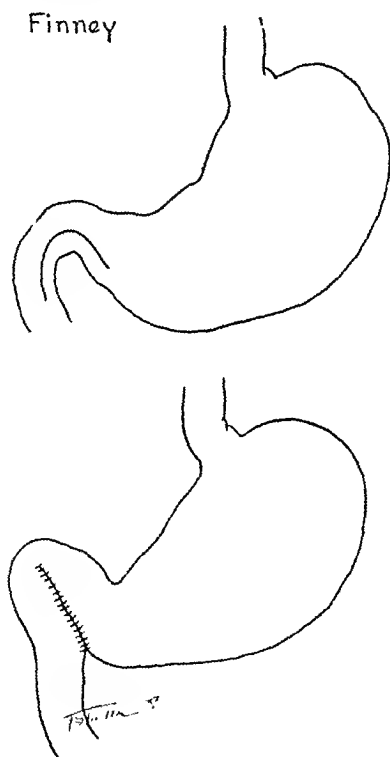


FIG. 10.

In this way practically the whole of the first and second, and even, if necessary, the third, portions of the duodenum may be readily mobilized with a minimal amount of bleeding. (The reasons for this have been discussed earlier.) After the pylorus and duodenum have been thoroughly freed, three guide and tractor sutures are placed: one at the upper margin of the pylorus; one in the wall of the stomach close to the gastrocolic omentum and about three inches from the pylorus, on the greater curvature; the third along the free border of the duodenum and a corresponding distance distal to the pylorus. By approximating these last two guides with slight traction downward and at the same time



intestinal walls may be so edematous and friable as to make proper stitching most difficult, if not impossible. One practical point, which will make closure easier in any event, is to have previously freed the upper surface of the pylorus, as well as the cap and first portion of the duodenum from its attachment to the veillike suspensory ligament and the lateral border of the gastrohepatic omentum.

The Mayo modification consists of a somewhat longer and crescentic rather than linear incision, making it easier to excise an ulcer, if present.

The Horsley modification, 1919, stresses the excision of any ulcer present and emphasizes the fact that the incision, which is linear, should

Mayo Modification

Horsley Modification

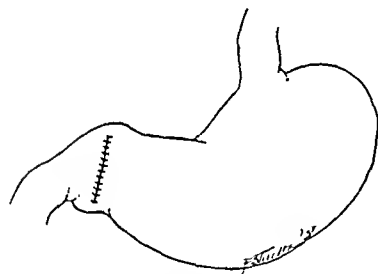
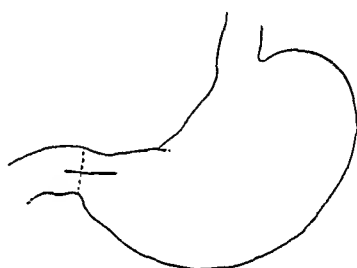
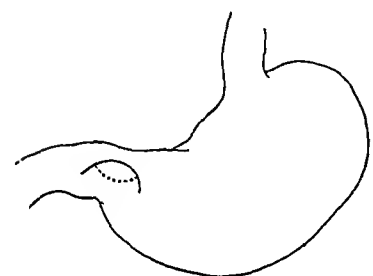


Fig. 8.

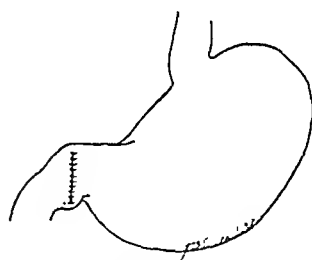


Fig. 9.

extend twice as far on the stomach as on the duodenal side of the pylorus, and never be over three inches in total length. In his closure, he is very careful not to include the pyloric mucosa in any stitches, or injure it by handling, as he feels such trauma is a potent cause of recurrent ulcer.\*

In 1902, Finney first described his pyloroplasty, or, as it is sometimes called, "gastropyloroduodenostomy," a title which possibly better suggests its greater extent and wider application. It has since been modified somewhat by its originator and his associates. Such modifications have consisted mainly in methods of suturing and have not affected

\*We have not included the so-called Judd pyloroplasty, which involves the resection of the anterior portion of the pyloric sphincter through an incision in the line of its fibers, and closure in a similar transverse (to the bowel) direction, because we feel that it is primarily a resection of muscle rather than a plastic operation in the true sense of the word.

the underlying principles of the operation. The abdomen is opened by a high right rectus incision, curving the upper end medially along the costal margin, if necessary, to gain proper exposure in cases where the duodenum and pylorus are lying in a high transverse position. Careful examination is then made of the local lesion and its suitability to this type of operation is determined. The superior margin of the duodenum just beyond the pylorus, and occasionally including it, is freed from any adhesions and from the supporting ligament running to the undersurface of the liver. This is done by a small incision along the duodenal margin, followed by peeling out the duodenum bluntly with the fingers, aided at times with gauze, or rarely by sharp dissection.

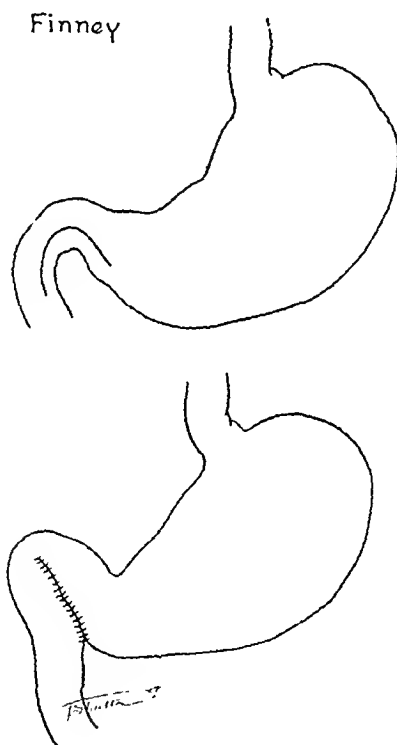


FIG. 10.

In this way practically the whole of the first and second, and even, if necessary, the third, portions of the duodenum may be readily mobilized with a minimal amount of bleeding. (The reasons for this have been discussed earlier.) After the pylorus and duodenum have been thoroughly freed, three guide and tractor sutures are placed: one at the upper margin of the pylorus; one in the wall of the stomach close to the gastrocolic omentum and about three inches from the pylorus, on the greater curvature; the third along the free border of the duodenum and a corresponding distance distal to the pylorus. By approximating these last two guides with slight traction downward and at the same time

supporting the pylorus by like traction upward on the one first placed, the walls of the stomach and duodenum should virtually fall in apposition for the placing of the posterior suture. This is of fine black silk (or catgut if preferred); it is usually most easily placed with a fine curved intestinal needle. The suture which we commonly employ is a simple continuous one, beginning at the lower margin of the pylorus and running downward to the traction sutures, and inserted well back toward the vessels of the greater curvature of the stomach and mesentery of the duodenum, endeavoring to catch such vessels as are visible in or on the wall of stomach and bowel, so as to reduce the amount of bleeding to be encountered later on when the incision is made through these walls. When this stitch has been satisfactorily placed, it will leave about three-quarters of the circumference of the duodenum for the placing of the mattress sutures. These, also of fine black silk, are then inserted, starting from the lower end of the posterior suture just described, and overlapping that end a bit so as effectually to seal this angle. The mattress sutures are placed far enough out from the posterior row, so as to include any ulcer which may be situated on the anterior or upper portion of the duodenum to allow of its excision later. These mattress sutures are next loosened and retracted, one-half downward, the other half upward, and thus held well out of the operative field. By inserting the anterior stitches before opening the stomach and duodenum, they can be placed just where wanted so much more easily. (As a matter of fact the author does not follow this step of the originator, but opens the bowel without the previous insertion of anterior stitches; then, when the time comes for closure, doing so with two rows of continuous stitches as posteriorly; the first a Connell suture of fine catgut, the second an overlying continuous suture of fine silk.) The general abdominal cavity is now thoroughly packed off from the region of operation and the wound edges protected by wet pads before making the incisions into stomach and bowel. Beginning from below, on the stomach side about one-half centimeter from the lower end of the posterior suture line, and being careful to include all layers of the stomach wall, we carry the incision upward and, through the pylorus, down into the duodenum, in the shape of a narrow inverted U, to a point opposite the start on the stomach side. This will give approximately a two and one-half inch incision in the anterior wall of each viscus connected by a division of the pyloric sphincter. If there is an ulcer on the anterior or superior portion of the pylorus or duodenum it should be excised, ample room having been allowed for this in placing the mattress sutures, as stated above. If the ulcer is situated on the posterior wall of pylorus or duodenum, it will be somewhat more difficult of excision. But this can be accomplished by removing a triangular piece of the duodenal wall (including pyloric muscle or not, as indicated or desired), apex downward toward the posterior suture. If such a procedure is necessary, we complete the

closure of the defect in the posterior wall, so made, before that of the pyloroplasty proper. A running suture of fine catgut is started at the point from which the apex of the triangular piece was removed, and the mucosa and muscular layers of the stomach and duodenum are brought together. We find it advisable to use a buttonhole lock stitch for this, as it adapts itself best to the conditions. The restored superior wall of the duodenum is then retracted downward and a continuous fine silk reinforcing suture is placed in the serous surface, running upward and over the superior curvature as it has been reconstructed. When these two sutures have been completed, we have returned to the status quo ante. (If it does not seem advisable or feasible to excise such a full thickness portion of the superior or posterior wall, as for instance in the presence of dense adhesions to or apparent perforation into the head of the pancreas, the ulcer may be removed, destroyed, or covered over as indicated in the description of the Heineke-Mikulicz pyloroplasty.) Looking through the incisions in the anterior walls, into the opened stomach and duodenum, we start a fine catgut suture at the lower angle posteriorly and make a continuous through-and-through buttonhole stitch, approximating the cut edges of mucous membrane and muscularis of stomach and duodenum. This gives a smooth closure of the posterior wall and controls all bleeding there. The bleeding points of the anterior wall of both stomach and duodenum should be individually clamped and tied. Sometimes at the upper end of the posterior suture line, where the fibers of the pyloric sphincter have been cut across, there may be some redundancy of tissue. If this seems excessive, it may be trimmed off, being careful not to cut the posterior silk suture, first laid. We have found, however, that this ridge will rapidly flatten out and disappear if left alone. There is, at this stage of the operation, a posterior wall which is held solidly by a serous continuous suture of silk and a muscular and mucosal continuous suture of catgut. The posterior line having thus been completed and all bleeding on the anterior edges having been checked, the mattress sutures previously laid are drawn taut and tied. This row is reinforced by a second one of Lembert sutures of fine silk, completing the anastomosis. (Personally, as indicated above, we complete the anterior closure by a continuous Connell suture of fine catgut, which is started at the lower angle, and then cover this with a continuous suture of fine silk, also started at the lower angle.) The anterior suture line may then be reinforced, if desired, by fat from gastrocolic or gastrohepatic omentum, or by bringing up the greater omentum and tucking it well up in the angle between the undersurface of the liver and the superior portion of the duodenum. The abdominal wound is closed in layers, without drainage.

#### RESECTIONS WITH GASTRODUODENOSTOMY

The first successful resection of the pylorus, which was completed by an end-to-end anastomosis of stump of stomach to stump of duodenum

(the first gastroduodenostomy), was done by Billroth in 1881, and a report of it, together with two other similar cases, was published by Wölfler later that same year. Curiously enough, one of the great bones of contention concerning the technique of the anastomosis had then already been unearthed: whether the stump of the duodenum should be set into the stump of stomach at the greater or lesser curvature border. The reasons which Wölfler gave in this original report for switching to the lower position for implantation seem to us to be equally potent today. "In the second case, due to dilatation of the stomach, and the somewhat changed direction of the incision, the occlusion suture from the greater curvature upward formed a cul-de-sac which was exaggerated by the position of the anastomosis, high on the lesser curvature. The third resection was based on my experiments on the cadaver, which

### Billroth I

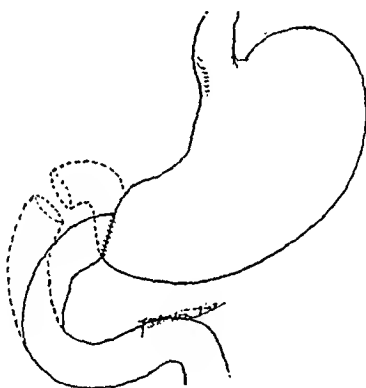


Fig. 11.

showed that we should attach the duodenum at a point near to the greater curvature instead of near the lesser curvature. This was for the purpose of avoiding a diverticulum of the fundus of the stomach as well as for providing more favorable conditions for the outflow of stomach contents. . . . If it is feared that by joining the duodenum at the greater curvature a diverticulum may form at the lesser curvature, it may be more satisfactory to make the incision obliquely through the stomach wall from above and from the left downward and to the right. Under all conditions the oblique division of the stomach appears to be the most satisfactory for avoiding diverticula. In future cases, therefore, Professor Billroth would, whenever possible, insert the duodenum into the greater curvature." Mechanically this placement seems more preferable to us and is used whenever an end-to-end anastomosis is employed. W. J. Mayo also strongly recommends it, where the ratio of difference between stomach and duodenal orifices is greater than 2 to 1;

where less than that, the larger stomach may be pleated, and thereby reduced, by taking two stitches in it to every one in duodenum, rendering possible without reduction, a direct anastomosis. Another method for meeting the disparity between the two stumps involves a longitudinal incision in the anterior wall of the duodenum running back about an inch from the cut margin, which materially enlarges the open end and lessens the inequality with the stomach. We feel, however, that this endangers the blood supply of the terminal portion of the duodenum somewhat and consequently makes sloughing at the suture line posteriorly more likely. Horsley has been a proponent of setting in the duodenum at the lesser curvature, for he feels that there is less disturbance to the main nerve control of the left vagus, which is distributed along the lesser curvature, and that also this arrangement better maintains the *sulcus gastricus* or *Magenstrasse* for the emptying of fluids. There has been much reference to the "dangerous angle," where the reduction suture in the stump of stomach merges into the circular suture which attaches the duodenal stump, but we can see no reason why a leak here should occur any more readily than elsewhere in the suture line, provided there is no sloughing. This brings up the point of preservation of the blood supply of the duodenal stump, which we fear is often imperiled by too great effort on the surgeon's part to clean all gurry off the serosa before the anastomosis is made and by the use of too many tissue-constricting stitches in his effort to avoid the very thing which he is thereby fostering. Two rows of stitches if properly placed should render any bowel suture gas and water tight; more rows than that tend unduly to endanger blood supply and to invert an unnecessarily large flange of tissue.

In the technique of the pylorectomy, we follow pretty closely the principles laid down by W. J. Mayo in his article published in 1923. "The success of the procedure depends on early ligation of the gastric artery as close as necessary to the coeliac axis, depending on the location of the growth in the stomach (and the amount of that organ to be removed). After separating the gastrophatic omentum from the undersurface of the liver, the distal end of the gastric artery is held taut and the artery, glands, fat and underlying structures are dissected from the lesser curvature toward the pylorus, the lateral vessels being caught and tied in succession as the holding bands are cut." The gastrosplenic omentum has previously been freed from the greater curvature, opening the lesser peritoneal cavity. The stomach is then divided between rubber-shod clamps applied above the growth and somewhat obliquely, division usually being made with the canter. A running mattress suture of catgut is then started at the upper end on the lesser curvature and extended downward until the remaining unsewed portion of the stump of the stomach is only slightly larger than the apparent diameter of the duodenum. The stitch is then locked

and laid aside. A continuous running suture of fine silk is then started, also at the lesser curvature, covering and turning in the eatgut suture just completed; it is carried the same distance and also locked and laid aside. The distal stump of the stomach is now raised and turned back toward the right, and the posterior portion of the pylorus and immediately adjacent duodenum freed from the structures behind, particular care being taken not to injure the middle colic artery, the head of the pancreas, the common duct, and the hepatic vessels. Using this free end of stomach as a handle now, we approximate the posterior walls of the duodenum, just below the pylorus, and the remaining open portion of the stump of stomach by a continuous running suture of fine silk, which is tied at the lower margin. The duodenum is then severed about one-half of a centimeter proximal to this suture line. The eatgut stitch, which has been used to reduce the lumen of the stomach

### Kocher

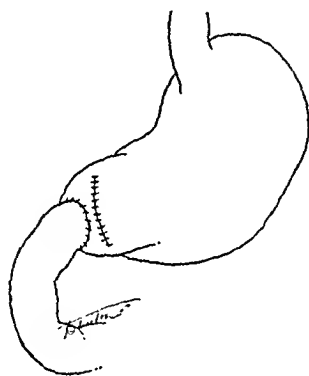


Fig. 12.

stump and then laid aside, is now continued as a buttonhole lock-stitch uniting muscularis and mucosa of stomach and duodenum to complete the posterior line, and, when the lower margin is reached, is still continued as a Connell suture up the anterior wall to the superior margin of the anastomosis, where it is tied with knot inverted. The running silk suture from above, which was also locked and laid aside, is now continued downward, anteriorly, making the second suture row here, and completing the anastomosis when tied at the greater curvature margin. The rents in gastrohepatic and gastrocolic omentum are now repaired, and the abdomen closed without drainage. But, as Mayo cautions, "This operation should not be forced. If it cannot be done easily, one of the other methods of gastrectomy should be applied. . . . The Billroth I operation is again coming to the front, not only for cancers located in the pyloric end of the stomach, but also for many ulcers on the lesser curvature. Instead of removing an unnecessary

sarily large area of the stomach as in the other forms of partial gastrectomy, it removes the disease, saves the normal stomach, and restores the gastrointestinal canal by uniting duodenum to the amputated end of the stomach."

In the Koehler modification, reported in 1893, the stump of the duodenum, following the pylorectomy and complete closure of the stump of the stomach, is implanted into the posterior wall of the stomach about one to one and one-half inches from its closed end, and near the greater curvature margin. This was suggested in order to eliminate the dangerous angle. So far as we know, it is rarely, if ever, used to-day.

Pursuant to the principles of his pyloroplasty and merely enlarging on them somewhat, Finney, about 1920, began using an end-to-side gastroduodenostomy following pylorectomy. After employing this

Haberer-Finney

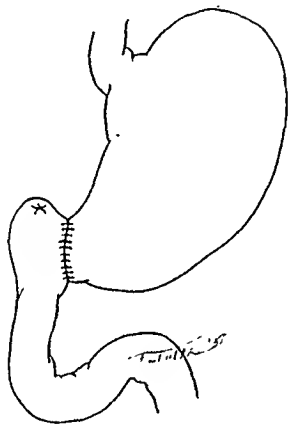


Fig. 13.

method satisfactorily several times, and while an article was in preparation to report it, one by von Haberer was published in 1922 describing an identical procedure which he had evolved independently. Finney's article appeared in 1923, so we have called this terminolateral gastroduodenostomy the Haberer-Finney modification of the Billroth I. Its advantage over the latter is that the surgeon is not limited in the size of the anastomotic opening by the diameter of the duodenum; hence the danger of constriction by circular scar contraction is completely eliminated. Also there is less danger of interference with circulation in the duodenal stump, with consequent sloughing and leakage. Its disadvantage is the extent of mobilization of the duodenum necessary to its proper performance; this objection is more apparent than real, however, if the principles laid down in the first part of this paper are remembered. This mobilization should be done before the pyloric resection is instituted. The pylorectomy is then done



as described for the Billroth I, the narrowing of the lumen of the stump of the stomach being carried out or not as the operator sees fit and to such extent as he desires. (We have arbitrarily adopted as our standard a lumen for the completed anastomosis which will readily admit the tips of three fingers—approximately two and one-half inches.) The duodenum is now severed and the stump inverted with a purse-string suture (much as the stump of the appendix in appendectomy), and this is reinforced with several mattress sutures of fine silk. The posterior wall of the gastric stump is then applied to the side of the duodenum, about three-quarters of an inch below its closed stump and united with a continuous running suture of fine silk, serosa to serosa. One may then lay an anterior row of silk mattress sutures, as in the original pyloroplasty, and retract them upward and downward out of the way, or proceed to open the duodenum, without this step. Bleeding points

#### Jaboulay

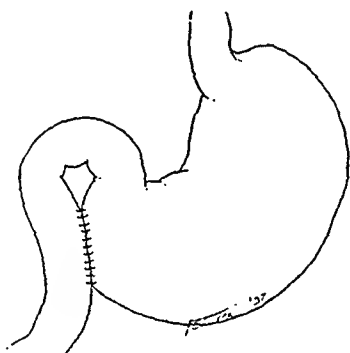


Fig. 14.

are clamped and tied, individually. Two sutures of fine catgut are now started in the center of the posterior wall, uniting muscularis and mucosa of stomach and duodenum by a buttonhole lockstitch, one running upward, the other downward. When the angles are reached, these are continued downward and upward as a Connell stitch in the anterior walls, until they meet at the center; here they are tied, throwing the knot inside. The mattress sutures of silk, previously laid and drawn aside, are now tightened and tied, and reinforced with intervening Lembert sutures of fine silk. If this step has been omitted above, a silk suture is started at either the upper or lower angle, and a running suture with it completes the anterior layer. The abdominal wound is closed without drainage.

There is one other type of gastroduodenostomy, a subpyloric side-to-side anastomosis which was first suggested by Jaboulay in 1892. This has a rather restricted field of application and is probably very infre-

quently used, but has certain merits, we feel, which might render its more frequent consideration advisable. To those who believe that marginal ulcers following gastrojejunostomy are a real hazard, and that both anatomy and physiology of digestion are better maintained by having stomach empty into duodenum rather than jejunum, we recommend it for trial in those cases where dense scarring and adhesions binding pylorus to undersurface of liver, to pancreas, and to common duct render proper mobilization of the pylorus and first portion of duodenum impossible for pyloroplasty. In many of these cases it is quite easy to free the second and third portions of the duodenum so that it can be approximated easily to the greater curvature of the stomach anterior to the attachment of the gastocolic omentum without any tension. Here a lateral anastomosis is performed after the technique just described for the Haberer-Finney gastroduodenostomy—two-layer suture of catgut and silk. This short-circuits below the pylorus and ulcer, if present, as does a gastrojejunostomy. It does away with the possibility of a kink at the site of anastomosis, a constriction by, or other difficulties with, a short transverse mesocolon, or a distended proximal loop instituting a vicious circle. And we have never heard of a marginal ulcer following this operation. In very thin individuals with a maximum degree of ptosis, it may be contraindicated from the possibility of a gastromesenteric ileus, which would still obstruct the bowel below the new stoma.

So much for the history of and the technique in performing the various pyloroplasties and gastroduodenostomies. Now what are their advantages and disadvantages in comparison with other forms of gastrointestinal anastomoses? First, they admit of the thorough examination of the lesion and adjacent lining of both stomach and bowel, together with the local removal of that lesion and consequent control of hemorrhage from it. This a simple gastrojejunostomy can in no wise do; a resection with a Polya type of anastomosis can do equally well. Second, when confronted by a perforated ulcer near the pylorus, some form of pyloroplasty is usually applicable, again allows of excision of the ulcer, and limits the extent of the operative field to the locality of the origin of the soiling, which may or may not make a difference. If a gastrojejunostomy is done, we are bound to spread things in turning up the omentum and transverse colon to get to Treitz's fossa. Third, a pyloroplasty or gastroduodenostomy, without resection, enlarges the opening of stomach into duodenum, and in all but the Jaboulay type, divides the sphincter and puts it completely out of commission in so doing, thus allowing free transfer back and forth of acid stomach and alkaline duodenal secretions to neutralize each other, and further lowering the acid manufactured by the stomach by allowing it to empty more rapidly. In gastrojejunostomy this is comparably true only when the pylorus is completely occluded; otherwise, though the

as described for the Billroth I, the narrowing of the lumen of the stump of the stomach being carried out or not as the operator sees fit and to such extent as he desires. (We have arbitrarily adopted as our standard a lumen for the completed anastomosis which will readily admit the tips of three fingers—approximately two and one-half inches.) The duodenum is now severed and the stump inverted with a purse-string suture (much as the stump of the appendix in appendectomy), and this is reinforced with several mattress sutures of fine silk. The posterior wall of the gastric stump is then applied to the side of the duodenum, about three-quarters of an inch below its closed stump and united with a continuous running suture of fine silk, serosa to serosa. One may then lay an anterior row of silk mattress sutures, as in the original pyloroplasty, and retract them upward and downward out of the way, or proceed to open the duodenum, without this step. Bleeding points

#### Jaboulay

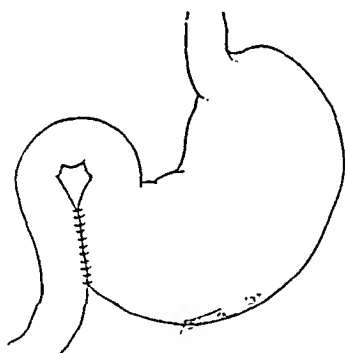


FIG. 14.

are clamped and tied, individually. Two sutures of fine catgut are now started in the center of the posterior wall, uniting muscularis and mucosa of stomach and duodenum by a buttonhole lockstitch, one running upward, the other downward. When the angles are reached, these are continued downward and upward as a Connell stitch in the anterior walls, until they meet at the center; here they are tied, throwing the knot inside. The mattress sutures of silk, previously laid and drawn aside, are now tightened and tied, and reinforced with intervening Lembert sutures of fine silk. If this step has been omitted above, a silk suture is started at either the upper or lower angle, and a running suture with it completes the anterior layer. The abdominal wound is closed without drainage.

There is one other type of gastroduodenostomy, a subpyloric side-to-side anastomosis which was first suggested by Jaboulay in 1892. This has a rather restricted field of application and is probably very infre-

cinomas. With ulcers of this type and in this location we almost invariably have a fairly high degree of free acid, usually considerably more than normal. We have repeatedly shown, at least to our own satisfaction, by cultures taken from both stomach and duodenum at the time of operation, that a stomach properly prepared by fasting and lavage will sterilize itself within twenty-four hours so far as pathogenic bacteria are concerned; we usually demand a forty-eight-hour period of preoperative preparation. From all of this we can reasonably conclude, we believe, that the hemorrhage may not be entirely undesirable after all, and the soiling more imaginary than real. So far as forms of anastomoses following pylorotomy are concerned, soiling and hemorrhage should not differ whether gastroduodenostomy or some other method be used. Conversely, it is the contention in certain quarters that the trauma done to mucosa by the ill-advised or improper use of clamps may be a potent factor in the recurrence of ulcer. Partly for this reason, partly for those given above, we rarely use compression clamps when doing a simple posterior gastroenterostomy. Eighth, one is limited in the extent of resection by employment of a gastroduodenostomy for closure. This is mainly, though not entirely, true. The degree of mobility of duodenum is sometimes surprising; we have twice joined esophagus to duodenum following complete gastrectomy; once end-to-end, once end-to-side. In the main, though, a terminolateral gastrojejunostomy is easier and preferable after extensive resection.

In conclusion, it is only fair to say that we will admit that we are prejudiced in favor of pyloroplasty and gastroduodenostomy, but we hope not unreasonably so. We do strongly advocate the more general understanding of the underlying principles and technique involved, in the belief that such knowledge will furnish further weapons in the armamentarium of the surgeon when he is called upon to face the fascinating problems presented in gastroenterologic surgery.

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anastomotic stoma be much larger than the pylorus, and though it be situated in a position to give, apparently, dependent gravity drainage, a certain amount will go through the natural channel, that amount being determined seemingly only by the degree of patency of the pylorus. In so doing, its acid content neutralizes the alkalinity of the duodenal secretions so that there is correspondingly less protection afforded the mucosa in the region of the new jejunal stoma, and the passage of such acid material as comes directly through it renders the incidence of marginal ulcer that much higher. This would seem to explain the fact which most surgeons recognize, that the greater the patency of the pylorus, the less satisfactory the results from gastrojejunostomy. Fourth, pyloroplasty does not remove the ulcer-bearing area. Neither does gastrojejunostomy. Only a pylorectomy does this, and we question whether such a reason is adequate justification for the constant employment of the more radical procedure. Granted that it is valid reasoning, however, we believe that gastroduodenostomy offers a better type of reconstruction than gastrojejunostomy of Polya or others. Fifth, pyloroplasty does not decrease the acid-forming area of the stomach; neither does simple gastrojejunostomy. Only a very extensive resection of the stomach will accomplish this, and we feel sure such operation is rarely justified in any case of simple ulcer. Sixth, pyloroplasty is claimed by some to be technically much more difficult than simple gastrojejunostomy. This we feel is at least debatable. We will grant that it has certain limitations, depending mainly on mobility of duodenum, beyond which it certainly should not be pushed. On the other hand, if the principles of mobilization are thoroughly understood and practiced, the field of applicability will be found quite wide. And also, there are cases where a short, excessively fat transverse mesocolon renders the performance of a posterior gastrojejunostomy technically exceedingly difficult or altogether impossible. The great advantage which it holds is that it is much more universally taught and hence better understood. Anything which is not thoroughly comprehended appears more difficult. Seventh, there is much more bleeding and soiling with pyloroplasty. This is true because most surgeons use clamps in doing gastrojejunostomies. But is all the disadvantage on one side here, and does it really make much difference? When stomach or bowel is opened without clamps having been previously applied, we see the bleeding points, clamp them, and tie them; we do not depend on suture lines for hemostasis. The result is that we have not been bothered by cases of postoperative gastric or intestinal hemorrhage. Apparently such things do occur at times after other types of operations, for we have been asked on numerous occasions how we treat them. As for the soiling, pyloroplasties are done for either gastric or duodenal ulcers, near the pylorus and presumably with a certain degree of pyloric stenosis; they are not done for car-

## SHOULD GASTRIC RESECTION BE DONE FOR DUODENAL ULCER?\*

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MY INTEREST in the problem of whether gastric resection should be done for duodenal ulcer dates from that time in the early 1920's when Finsterer, visiting various surgical clinics in the United States, strongly advocated gastric resection as a routine method of treating duodenal ulcer in order to eliminate gastrojejunal ulceration. A similar viewpoint had been taken by Lorenz, another Viennese surgeon. Although it had been the custom in the Mayo Clinic as early as 1905<sup>14</sup> to perform partial gastrectomy in the treatment of large, calloused gastric ulcers because of the possibility of the lesion's being malignant, the more conservative procedures of gastroenterostomy or excision of the duodenal ulcer, with plastic operations involving the lower portion of the stomach and the duodenum, had been the surgical procedures of choice for patients with duodenal ulcer who had failed to obtain relief of symptoms on a medical regimen.

### GASTROJEJUNAL ULCERATION

My recollection is that, at the time in the early 1920's of which I have spoken, Finsterer's main reason for advocating gastric resection for duodenal ulcer was that it was followed by reduction in the incidence of gastrojejunal ulcers to 1 per cent or less, in contrast to a reported incidence of 10 per cent subsequent to gastroenterostomy performed in Austria. The reason for this reduction in the occurrence of gastrojejunal ulcer was stated to be that achlorhydria occurred subsequent to gastric resection and hence recurring ulceration, gastrojejunal in character, could not take place. However, since the risk of partial gastrectomy was greater than that of gastroenterostomy, and since in partial gastrectomy the considerable part of the stomach that was removed, when examined by the pathologist, usually did not give evidence of any particular disease, and further, since the incidence of recurring ulcer after the conservative operations of gastroenterostomy or pyloroplasty had been followed in many clinics by an incidence of recurrent ulceration of not more than 4 per cent, little enthusiasm was aroused in the United States for partial gastrectomy in the treatment of duodenal ulcer. There were, however, two groups of surgeons in

\*Read before the meeting of the Western Surgical Association at Kansas City, Mo., December 11 and 12, 1936.

Received for publication, December 29, 1936.

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others who emphasized the high incidence of gastritis associated with duodenal ulcer found among German surgical patients; and it was thought by these observers that gastritis was the forerunner of the development of the duodenal ulceration. This high incidence of ulcerative hemorrhagic gastritis, stated to be characteristic of from 99 to 100 per cent of German patients operated on for duodenal ulcer,<sup>8, 9</sup> led Snell and me, in 1931, to visit various surgical clinics in Germany, Austria, and Hungary. In studying the resected portions of the stomachs of patients operated on for duodenal ulcer in these countries, as well as specimens previously removed by Schmieden at Frankfurt, Snell and I were impressed by the high incidence of gastritis present in the German cases in contrast to the very low incidence of gastritis associated with duodenal ulcer among patients on whom I had operated at the Mayo Clinic. These observations were published in a series of papers in the years 1931 to 1933,<sup>4, 18, 20, 21, 22, 24</sup> and the accuracy of the observations was confirmed by Sebening,<sup>18</sup> of Schmieden's Clinic, who spent several months in study at the Mayo Clinic. The very infrequent occurrence of gastritis among patients operated on at the Mayo Clinic for duodenal ulcer, in comparison with those operated on at the German clinics, is probably explained on the basis of so-called geomedical variation of types of lesions and by the part played by racial factors in these differences, which has been commented on by von Haberer and more recently by Schittenhelm. The latter, gathering data from various parts of Germany, has emphasized the fact that disease frequently presents different characteristics, even in localities where it first appeared. Quoting briefly from Schittenhelm's report: "Apoplexy, atherosclerosis, and thrombosis are more frequent at Basel than at Kiel. Gastric and biliary disorders likewise present distinct regional differences—the part played by racial factors in these differences is as yet unknown to science." Further lending support to the geomedical differences in gastritis associated with duodenal ulcer is the fact that in a paper published by Aschner and Grossman, gastritis was found in approximately 60 per cent of the portions of stomach resected for duodenal ulcer, in contrast with its presence in less than 12.5 per cent of the series of resected gastric specimens on which I reported from the Mayo Clinic where, in a series of cases, partial gastrectomy had been performed for duodenal ulcer.<sup>4, 24</sup> The corollary of this would seem to be, therefore, that since, in our experience, gastritis has been such an infrequent accompaniment of duodenal ulcer, any argument directed toward the value of removing such areas of gastritis in the performance of partial gastrectomy for duodenal ulcer could not be used in favor of such a procedure in the cases in which we usually operate.



two separate areas of the United States, who had adopted the procedure. One of these groups had adopted it, since in their experience a relatively high incidence of gastrojejunal ulceration occurred following more conservative procedures.<sup>10,11</sup> Their patients were, for the most part, of one race in which the percentage of intermarriage is exceedingly high. In the years that followed, largely as a result of the interest of these two groups of men who, in their experience, had been able to reduce the incidence of gastrojejunal ulcer in their cases to 3.1 per cent<sup>3</sup> as a result of the adoption of partial resection for duodenal ulcer, increasing interest in partial gastrectomy for duodenal ulcer appeared.

With the accumulation of larger series of patients on whom partial gastrectomy had been performed for duodenal ulcer, it became apparent that ulceration did recur even after subtotal gastrectomy. Usually the patients were found to have persisting free hydrochloric acid in the gastric content, and the erroneous conclusion was drawn that an insufficient amount of stomach had been removed. This opinion later was modified in this country, for in 108 cases in which partial gastrectomy or subtotal gastrectomy was performed for duodenal ulcer, relative achlorhydria occurred in but approximately 56 per cent.<sup>6</sup> Of greater significance, it seems to me, was the fact that in 44 per cent of the cases hydrochloric acid persisted or recurred in gastric secretion, and in nine cases gastrojejunal ulceration developed. In taking that reported series of 108 cases as a group, the incidence of gastrojejunal ulcer following partial gastrectomy was 8.3 per cent.<sup>7</sup> With the general recognition of the fact that gastroenterostomy carried a much lower surgical mortality<sup>2, 13, 15, 27</sup> than partial gastrectomy,<sup>3</sup> and of the fact that in our experience at the Mayo Clinic, as well as in the reports of other surgical clinics, gastrojejunal ulcer appeared in approximately only 3.2 per cent of cases,<sup>2</sup> we could not see the necessity for the routine performance of partial gastrectomy for primary duodenal ulcers on a comparative basis of formation of gastrojejunal ulceration. In this connection, it is worth while calling your attention to the report of a collective investigation,<sup>13</sup> in 1928, into the after-history of gastroenterostomy by the British Medical Association in respect to patients operated on in various parts of the British Empire during the period 1920 to 1924, inclusive. Quoting from this report: "Secondary gastrojejunal ulcer occurred in 2.8 per cent of 744 cases in which gastroenterostomy was performed for duodenal ulcer. . . . The postoperative mortality was 5 per cent. . . . The results of the operation were satisfactory in about 90 per cent of the cases."

#### GASTRITIS

The next wave of enthusiasm favoring partial gastrectomy for duodenal ulcer took its origin following the work of Konjetzny, Puhl, and

TABLE I

RELATIVE ACHLORHYDRIA OCCURRING IN SOME CASES OF DUODENAL ULCER AFTER GASTROENTEROSTOMY

CASE	AGE, YEARS, AND SEX	DURATION OF SYMPTOMS	CHARACTER OF ULCER	PREOPERATIVE ACIDITY		HISTAMINE INTERVAL, MINUTES								POSTOPERATIVE ACIDITY	
				TO-TAL	FREE HCl	10	20	30	40	50	60	70	TO-TAL	FREE HCl	
1	24 F	3 years	Subacute perforating with obstruction	40	34								14	0	
2	38 M	20 years	Subacute perforating	62	50								12	0	
3	48 M	12 years	Subacute perforating obstructing	76	70	Total 26 48 70 80 92 76 100 Free HCl 16 42 62 74 86 70 96								8	0
4	35 M	20 years	Acute perforating	100	80								14	0	
5	47 M	5 to 6 years	Subacute perforating	118	100								10	0	
6	47 M	35 years	Chronic (?)	60	40								16	0	
7	48 F	6 years	Subacute perforating	74	60								9	0	
8	44 M	12 years	Subacute perforating	64	54								12	0	
9	50 F	10 years	Recurring	42	30								14	0	

TABLE II

THE INFREQUENT OCCURRENCE OF RELATIVE ACHLORHYDRIA WHEN BILLROTH I-HABERER ANASTOMOSIS FOLLOWING PARTIAL GASTRECTOMY AND PARTIAL DUODENECTOMY IS PERFORMED FOR DUODENAL ULCER

CASE	AGE, YEARS, AND SEX	DURATION OF SYMPTOMS	CHARACTER OF ULCER	ACIDITY			
				PREOPERATIVE		POSTOPERATIVE	
				TOTAL	FREE HCl	TOTAL	FREE HCl
1	49 M	15 years	Subacute perforating hemorrhagic duodenal	46	32	18	8
2	56 M	8 years	Duodenitis	62	52	8	0
3	33 M	17 years	Gastrojejunal ulcer healed; duodenal	50	38	16	0
4	47 M	15 years	Perforating duodenal	70	64	54	40
5	32 M	10 years	Multiple duodenal with duodenitis	96	80	40	36
6	59 M	30 years	Chronic bleeding duodenal	40	20	32	20
7	35 M	14 years	Multiple subacute duodenal	34	24	56	44
8	27 M	5 years	Multiple chronic duodenal with duodenitis	88	78	28	20

contrast to the changes in acidity which follow similar procedures carried out in the treatment of gastric ulcer (Table III). Although I do not wish to discuss localized gastric ulceration in this paper, I do wish to say that the two lesions, that is, duodenal ulcer and gastric ulcer, should be sharply differentiated, not only because of their pathologic variations but because of the difference in their physiologic chemical

## PARTIAL GASTRECTOMY FOR DUODENAL ULCER

Having discussed and eliminated, I believe, the factor of gastritis as an indication for partial gastrectomy in the cases in which we have operated, and having stressed the low incidence of recurring ulceration in several series of cases following gastroenterostomy in contrast to a much higher incidence of recurring ulceration following partial gastrectomy in another series of cases, the important matter to be settled would appear to be just *what partial gastrectomy accomplishes in a better fashion than either gastroenterostomy or pyloroplasty*. That, it seems to me, can be answered rather briefly in the statement that it accomplishes greater reduction of free hydrochloric acid in the gastric

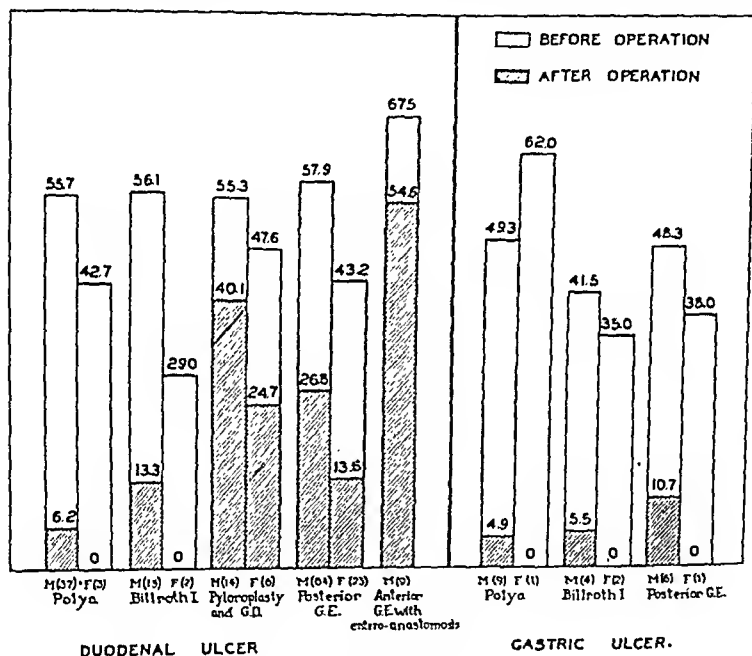


Fig. 1.—Mean (M) and free (F) gastric acidity, before and after operation in 194 cases.

secretion (providing the Polya type or Hoffmeister-Polya type of anastomosis is made) than does gastroenterostomy or pyloroplasty (Fig. 1). Although relative achlorhydria will more frequently occur following the Polya type of partial gastrectomy than following gastroenterostomy, yet it does occur following gastroenterostomy in some cases even if patients had high preoperative gastric acidity (Table I).<sup>23</sup> Of equal interest is the relative infrequency, in my experience, with which relative achlorhydria is obtained after gastric resection for duodenal ulcer when the Billroth I type of anastomosis is made; in other words, when the end of the stomach is sutured to the duodenum after resection of half or two-thirds of the stomach (Table II). This is in rather marked

that it is frequently difficult to tell in the preoperative study of the patient and of his nervous or gastrointestinal habitus, or in study of his gastric acidity, what his clinical response as regards relief of symptoms or changes in gastric acidity will be following any type of operation. For although a greater reduction of gastric acidity will occur and a greater number of patients will obtain relative achlorhydria after partial gastrectomy of the Polya type, marked reductions in gastric acidity, even to the point of relative achlorhydria, not infrequently will occur following gastroenterostomy. An enteroanastomosis made between the loops of the jejunum used in performing the gastroenterostomy or the Polya anastomosis will prevent some of the duodenal, pancreatic, and jejunal secretion entering the stomach, thus interfering in part with the dilution and reduction in gastric acidity (Table V).

TABLE V

PARTIAL LOSS OF THE DILUTION OF GASTRIC ACIDITY WHEN ANTERIOR GASTROENTEROSTOMY WITH ENTEROANASTOMOSIS IS PERFORMED FOR DUODENAL ULCER

CASE	AGE, YEARS, AND SEX	DURATION OF SYMPTOMS	CHARACTER OF ULCER	ACIDITY			
				PREOPER- ATIVE		POSTOPER- ATIVE	
				TOTAL	FREE HCl	TOTAL	FREE HCl
1	33 M	15 months	Subacute perforating	50	36	28	20
2	52 M	6 months	Subacute perforating	98	90	82	70
3	31 M	12 years	Subacute hemorrhagic per- forating	62	46	60	44
4	59 M	3 years	Subacute perforating	90	80	94	84
5	65 M	25 years	Subacute perforating	58	46	74	56
6	35 M	15 years	Hemorrhagic perforating	88	78	84	70
7	56 M	12 years	Subacute perforating	92	84	60	50
8	38 M	25 years	Multiple subacute perforat- ing	60	50	50	38

## TISSUE RESISTANCE

Such a discussion of gastric acidity is important, in spite of the fact that gastric acidity plays a secondary part in the formation either of a duodenal or a gastrojejunal ulcer. Tissue resistance or tissue susceptibility to inflammation or ulceration from the hydrochloric acid of gastric secretion is that on which successful surgical treatment of duodenal ulcer depends; for, if tissue is resistant to hydrochloric acid, the patient will obtain an excellent result from the recognized types of surgical procedures, without recurring ulceration; whereas if the tissue is susceptible to recurring ulceration, and if hydrochloric acid of the gastric secretion continues to be in contact with such susceptible tissue, ulceration may recur. Unfortunately, there is no way at present to measure, in vivo, individual intestinal tissue resistance to gastric secretion. Recent work at the Mayo Foundation by Stalker, Bollman, and Mann would seem to throw some light on this factor of tissue

TABLE III

RELATIVE ACHLORHYDRIA FOLLOWING PARTIAL GASTRECTOMY OF BILLROTH I TYPE

CASE	AGE, YEARS, AND SEX	DURATION OF SYMPTOMS	CHARACTER OF ULCER	ACIDITY			
				PREOPER- ATIVE		POSTOPER- ATIVE	
				TOTAL	FREE HCl	TOTAL	FREE HCl
1	53 M	7 months	Gastric	56	44	6	0
2	55 M	9 months	Chronic hemorrhagic perforating gastric	70	58	10	0
3	57 M	4 months	Ulcerating gastric lesion	64	52	8	0
4	49 M	3 months	Chronic gastric	52	40	60	0
5	57 M	6 weeks	Subacute perforating gastric and duodenal	54	30	8	0
6	58 M	4 years	Chronic gastric	28	16	36	22
7	50 M	30 years	Subacute perforating gastric	6	0	12	0
8	55 F	15 years	Perforating gastric	52	40	10	6

responses to the same types of surgical operation, particularly as regards gastric acidity. When partial gastrectomy, either of the Polya or of the Billroth I type, is performed for gastric ulcer, relative achlorhydria occurs almost without exception (Table IV), but only in ap-

TABLE IV

RELATIVE ACHLORHYDRIA FOLLOWING PARTIAL GASTRECTOMY OF POSTERIOR POLYA\* TYPE FOR GASTRIC ULCER

CASE	AGE, YEARS, AND SEX	DURATION OF SYMPTOMS	CHARACTER OF ULCER	ACIDITY			
				PREOPER- ATIVE		POSTOPER- ATIVE	
				TOTAL	FREE HCl	TOTAL	FREE HCl
1	47 M	2½ years	Subacute perforating gastric	76	60	4	0
2	58 M	4 years	Multiple gastric	48	30	20	0
3	44 M	8 years	Recurring subacute duodenal and gastric?	46	34	0	0
4	58 M	Several months	Subacute perforating gastric	60	42	10	0
5	56 M	1½ months	Subacute gastric perforating ulcerating			8	0
6	57 M	25 years	Obstructing gastric	40	30	5	0
7	40 F	31 years	Chronic gastric; chronic duodenal	38	24	4	0
8	58 M	3-4 years	Chronic perforating gastric	60	52	5	0

\*Hoffmeister-Polya type in Case 5.

proximately 60 per cent of reported cases when the Polya type of operations are performed for duodenal ulcer and less frequently still when the Billroth I type of resection is performed. In other words, in discussing any problem concerning peptic ulcer, careful differentiation should be made as to whether the ulcerating lesion is in the duodenum or stomach, or both.

The most interesting part of studies of gastric acidity subsequent to various types of operations for duodenal ulcer has seemed to me to be

that it is frequently difficult to tell in the preoperative study of the patient and of his nervous or gastrointestinal habitus, or in study of his gastric acidity, what his clinical response as regards relief of symptoms or changes in gastric acidity will be following any type of operation. For although a greater reduction of gastric acidity will occur and a greater number of patients will obtain relative achlorhydria after partial gastrectomy of the Polya type, marked reductions in gastric acidity, even to the point of relative achlorhydria, not infrequently will occur following gastroenterostomy. An enteroanastomosis made between the loops of the jejunum used in performing the gastroenterostomy or the Polya anastomosis will prevent some of the duodenal, pancreatic, and jejunal secretion entering the stomach, thus interfering in part with the dilution and reduction in gastric acidity (Table V).

TABLE V  
PARTIAL LOSS OF THE DILUTION OF GASTRIC ACIDITY WHEN ANTERIOR GASTROENTEROSTOMY WITH ENTEROANASTOMOSIS IS PERFORMED FOR  
DUODENAL ULCER

CASE	AGE, YEARS, AND SEX	DURATION OF SYMPTOMS	CHARACTER OF ULCER	ACIDITY			
				PREOPER- ATIVE		POSTOPER- ATIVE	
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resistance. These observers found that chronic penetrating gastric ulcers could be produced in 98 per cent of dogs by the oral or enteric administration of cinchophen. When the animals were given a bland, alkaline type of diet, frequently administered with alkaline powder similar to that used in the medical treatment of ulcer, in none of the animals which received cinchophen did chronic ulcers develop. Likewise, and of equal importance, was the fact that if gastroenterostomy was performed on animals which received cinchophen, chronic ulceration did not occur. When cinchophen was administered, the stomach divided, and the upper segment and jejunum anastomosed (exclusion type of operation), gastrojejunal ulcers occurred frequently in the upper segment and also in the lower, if enough of the acid-secreting gastric mucosa was included in the lower segment. In these experiments, one has the factor, not only of lower tissue resistance as a result of the cinchophen, but also of the action of gastric secretion on an area of lowered tissue resistance. These are exceedingly important groups of experiments and have, it seems to me, considerable clinical significance. They strengthen the conclusions relative to the beneficial effects of the alkalization of gastric secretion either as a result of the dietary regimen or of dilution and reduction of gastric acidity by gastroenterostomy.

What place, then, has partial gastrectomy in the treatment of duodenal ulcer? Theoretically it would appear that it has a place in the treatment of hemorrhagic duodenal ulcer, principally because it removes the bleeding lesion and is able to assure the patient a maximal degree of reduction of gastric acidity; yet in many cases of bleeding duodenal ulcer, gastroenterostomy suffices to heal the duodenal lesion. It has an important place in the treatment of recurring duodenal ulceration and in gastrojejunal ulceration. The reasons for its usefulness in this group of cases are similar to those for its usefulness in the treatment of bleeding ulcers, namely, that it removes the ulcerating lesions and gives the patient a maximal reduction of gastric acidity; but in addition, partial gastrectomy performed subsequent to previous operations for duodenal ulcer, whether pyloroplasty or gastroenterostomy, is followed by relative achlorhydria in a much higher percentage of cases than when partial gastrectomy is performed as a primary operation for duodenal ulcer. It will have a place in the treatment of the patient who has duodenal ulcer and whose tissue is abnormally susceptible to recurring ulceration from the irritating effects of hydrochloric acid in gastric secretion.

#### SUMMARY

Interest in partial gastrectomy for duodenal ulcer was stimulated by Finsterer's visit to the surgical clinics of the United States in the 1920's. The incidence of gastrojejunal ulcer following partial gas-

trectomy was reported to have been reduced to 3.1 per cent in one clinic in the United States. In that clinic the incidence of gastrojejunal ulcer was reported to have been 16 per cent following gastroenterostomy, this percentage being calculated on the basis of operations. It has been shown in some countries in Central Europe that by partial gastrectomy the surgeon removed areas of gastritis associated with duodenal ulcer, and Konjetzny reported the almost constant presence of gastritis in such cases. Such an argument favoring partial gastrectomy could not be used in deciding on treatment of a group of patients operated on at the Mayo Clinic, where definite evidence of associated gastritis was present in less than 12.5 per cent of a group of patients on whom partial gastrectomy was performed for duodenal ulcer.<sup>24</sup> The incidence of recurring ulceration following gastroenterostomy at the Mayo Clinic is 3.2 per cent,<sup>2</sup> in contrast to the greater incidence of recurring ulceration reported from the German surgical clinics and from one of the clinics in this country where partial gastrectomy for duodenal ulcer is advocated. This leads to the opinion that there is marked difference in the geomedical factors relating to types of lesions and their response to similar operative procedures. Quoting from Schittenhelm, the Munich internist: "Gastric and biliary disorders likewise present distinct regional differences—the part played by racial factors in these differences is as yet unknown to science." The operations of partial gastrectomy, gastroenterostomy, and pyloroplasty all serve to reduce gastric acidity; the greatest reduction occurs after the Polya type of operation, although not infrequently relative achlorhydria is obtained when gastroenterostomy is performed. It has been reported in one clinic in the United States that relative achlorhydria was not obtained in approximately 43 per cent of a group of 108 patients on whom extensive partial gastrectomy had been performed for duodenal ulcer, and nine patients developed gastrojejunal ulcer, an incidence of 8.3 per cent.

Tissue resistance and tissue susceptibility to hydrochloric acid, and their measurement, are the factors on which successful treatment of duodenal ulcer depends regardless of the surgical procedure employed, for, if tissue resistance to hydrochloric acid is satisfactory, ulceration will not recur, whereas, when tissues are susceptible to hydrochloric acid of the gastric secretion, ulcer may recur, if free hydrochloric acid persists in sufficient degree, regardless of the surgical procedure employed. Recent work at the Mayo Foundation by Stalker, Bollman, and Mann bears a relation to the factor of tissue resistance in formation of ulcer. Gastric resection has a place in the treatment of certain of the hemorrhagic duodenal ulcers as well as in the treatment of recurring duodenal ulcer and of gastrojejunal ulceration; it also is applicable in treatment of patients whose tissue has lowered resistance to the hydrochloric acid in gastric secretion.



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# ADENOMYOMA OF THE INGUINAL REGION

## REPORT OF THREE CASES

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(From the Mayo Foundation)

THE literature which has accumulated on aberrant endometrium-like tissue is evidence of the interest which this subject has aroused and of the attention it has been given by gynecologists and pathologists. It is certain that there is no subject in the realm of gynecology which has led to more controversy, and it is probably equally true that no other subject related to gynecology presents a more fascinating clinical and pathologic picture. Unless the clinician, surgeon, or gynecologist is familiar with the manifestations of ectopic endometrium-like tissue and the situations in which it is not infrequently found, he will in all probability fail to detect some lesions which should be easily diagnosed.

Rokitansky, Babes, Breus, and Diesterweg are said to have been the first to recognize epithelial cysts in myomas of the uterus. In 1896, von Recklinghausen first used the terms adenomyoma and cystadenomyoma to describe uterine and tubal swellings which he thought were derived from the wolffian duct. Sampson is usually given the credit for the introduction of the term endometriosis although it is said by some to have first been used by de Joselin de Jong, and some say that the two men introduced the term independently and simultaneously. For blood cysts of the ovary in which endometrium-like tissue can be demonstrated, Lockyer<sup>23</sup> said that Blair-Bell introduced the "convenient but not strictly correct nomenclature of endometrioma," a term which is currently used to designate similar lesions in any situation. These three terms, adenomyoma, endometriosis, endometrioma, are the ones most frequently employed to describe adenomatous lesions among women, the morphologic and functional manifestations of which are similar to those of the endometrium. The terms apparently are used synonymously but each has its adherents and its critics, and no term is considered ideal. When and if the etiology of this condition is definitely established, an appropriate name can be given to it.

In May, 1896 Cullen<sup>2</sup> described the first case of adenomyoma of the round ligament, a lesion previously unknown. His patient was a woman, aged thirty-seven years, who complained of swelling of the right inguinal region which had been present for eight years. It was severely painful, especially during the menstrual period and after exertion.

Received for publication, May 15, 1937.

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Nineteen months after the removal of the adenomyomatous mass, the patient returned with a similar one on the opposite side. This, too, was removed surgically. Each mass was attached to the round ligament and scattered throughout each mass were islands of glands lined with one layer of cylindrical epithelium. The glands could not be distinguished from uterine glands and the stroma was composed almost entirely of nonstriated muscle fibers.

Cullen<sup>7</sup> wrote in 1898 that 3 similar cases had been reported since the description and publication of his first case in 1896, and in 1908<sup>8</sup> he said that cases had been reported by Pfannenstiel, Blumer, Bluhm, Meyer, Aschoff, and others. Of the 26 cases of tumor of the round



Fig. 1.—Section of tumor found in Case 1; the endometrial glands are typical and the stroma is abundant; adipose tissue is present on the right side (x55).

ligament which he collected in 1903, Emanuel found several adenomyomas, and to this list he added 4 cases of his own. In reviewing tumors of the round ligament in 1914, Taussig collected 135 cases; in 30, or 22 per cent, of these cases the tumor was an adenomyoma. He commented that "the most striking fact in the pathology of round ligament tumors is the comparative frequency of adenomyoma"; these tumors were four times as frequent at this site as they were in 1,283 cases of myoma of the uterus collected by Cullen. Polster reported that in the literature prior to 1926 he could find but 34 cases of adenomyoma of the round ligament, but this figure, although quoted by most writers on this subject, is undoubtedly too low. Judd and Foulds listed three cases of adenomyoma of the groin in their series of 494 cases of adenomyoma. Harbitz said that R. Meyer had not observed

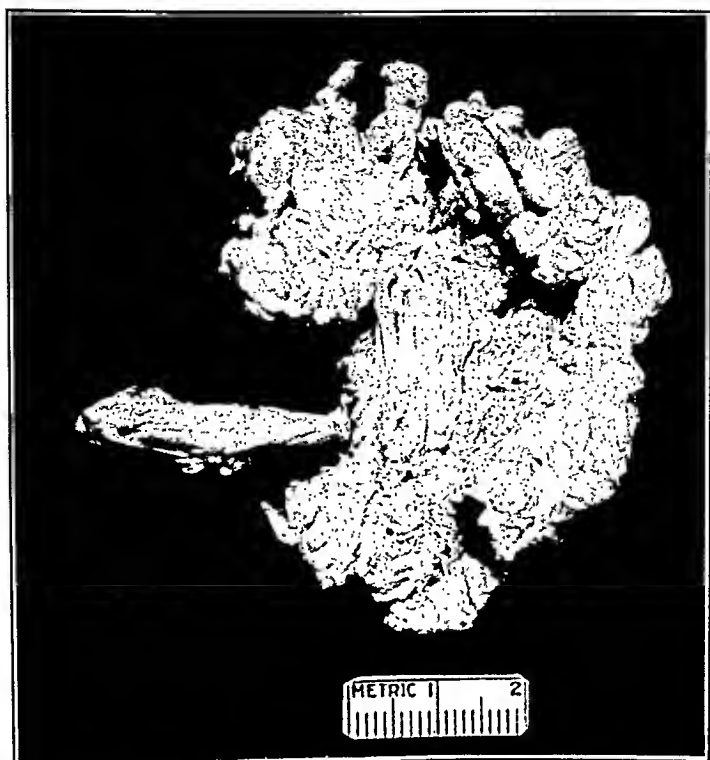


Fig. 2.—Tumor found in Case 2; round ligament is attached to the left side of the mass; tags of fat and fibrous septa are well illustrated.

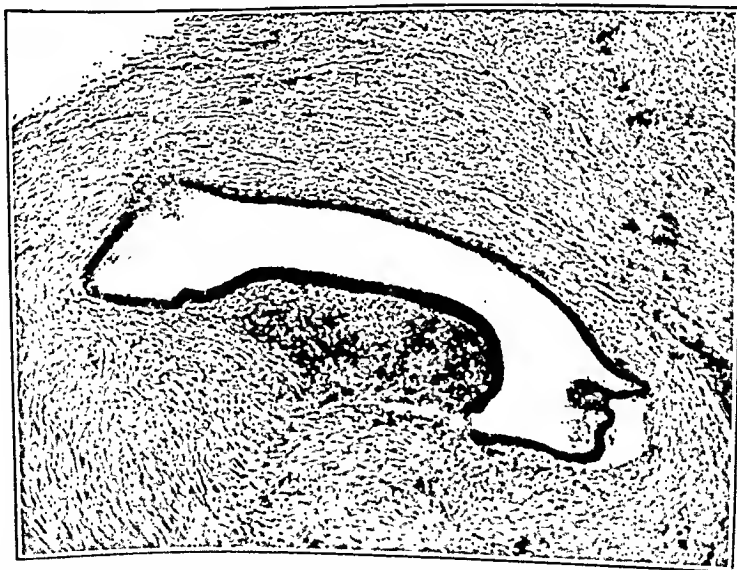


FIG. 3. Section of tumor found in Case 2; a large gland and stroma cells may be seen at the lower border; the epithelium adjacent to the stroma cells is much taller than that resting directly on the connective tissue or smooth muscle fibers ( $\times 50$ ).

more than 3 cases of so-called inguinal endometriosis of his own. In the 159 cases observed by Smith, the tumor was localized in the round ligament in only 1 case. Nielsen said that 60 to 70 cases of adenomyoma of the round ligament have been reported.

Mahle and MacCarty have reported 2 cases of adenomyoma of the groin from the Mayo Clinic and Lemon and Mahle reported an additional case. I wish to report the following cases; in all of these cases there was an inguinal tumor, and in 2 of them there was definite involvement of the round ligament.

#### REPORT OF CASES

CASE 1.—A married woman, aged thirty-five years, came to the clinic because of a lump in the breast, and a swelling in the right inguinal region, which had been present for eight years. The inguinal tumor was the size of an egg. It was firm and movable but was not reducible. It was situated over the external inguinal ring. Menses were regular and without pain.

At operation the tumor was found to be situated very close to the spine of the os pubis and, while it was not definitely attached to the round ligament, it was thought by the surgeon to be a cyst of the round ligament. It was completely removed.

The mass was firm in consistence although surrounded by adipose tissue. It contained much fibrous tissue and grayish bands traversed it. It measured 3 by 1.5 by 1.5 cm. The tumor of the breast unfortunately proved to be an adenocarcinoma, grade 4, and the patient died a little more than two years following the radical mastectomy.

Microscopic examination of the inguinal tumor (Fig. 1) revealed the typical picture of adenomyoma.

CASE 2.—A married woman, aged forty-four years, who was the mother of two living children, complained of a lump in the right inguinal region. Eighteen years before her registration at the clinic, a right herniorrhaphy had been performed. The incision had drained for four months but the character of the drainage was not stated. Menses had always been regular.

Soreness and pain had been present in the right inguinal region for six months, and four months before she came to the clinic she had noticed the lump. The symptoms had been more pronounced during menstruation.

A firm, movable, tender nodule was palpable just below the old herniorrhaphy scar over the spine of the pubis. Although the patient said that she had had a left inguinal hernia, this could not be demonstrated.

At operation the mass was found to be connected with the terminal portion of the round ligament; it was removed together with a portion of the ligament. There were bilateral indirect inguinal hernias. These were repaired.

The tumor measured 5 by 4 by 2.5 cm., and 2.5 cm. of the round ligament was attached to it. The tumor was firm in consistence and completely covered by fatty tissue. The cut surface was dark brown in color and was reticulated. The trabeculae were grayish in color and between them there were many small cysts filled with a dark fluid (Fig. 2).

The microscopic appearance was that of an adenomyoma (Fig. 3).

CASE 3.—A married woman, aged thirty-nine years, had undergone an appendectomy seventeen years before she came to the clinic. This had been followed by phlebitis in the right thigh. Two years prior to her registration at the clinic she

had had a postpartum infection following the delivery of a stillborn child. Menses had been regular and the interval between the menstrual periods had been twenty-eight days.

The patient complained of a pain over the right lower quadrant of the abdomen following each menstrual period; this symptom had first been noted just after the

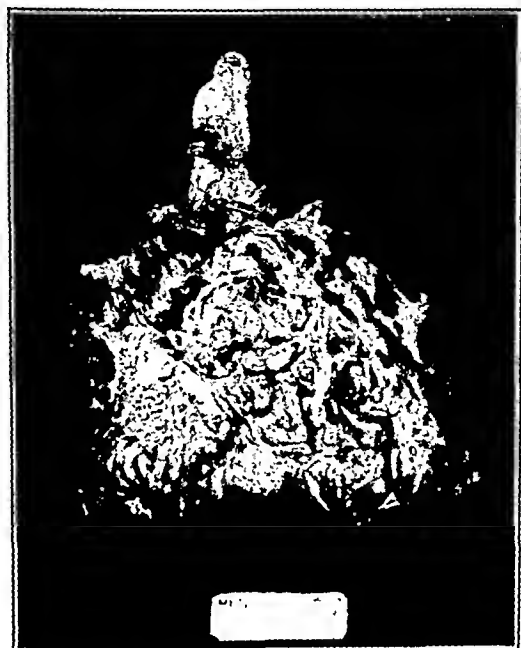


Fig. 4.—Tumor found in Case 3; round ligament is attached to upper part of the mass; tags of fat, fibrous septa, and even small cysts are visible.

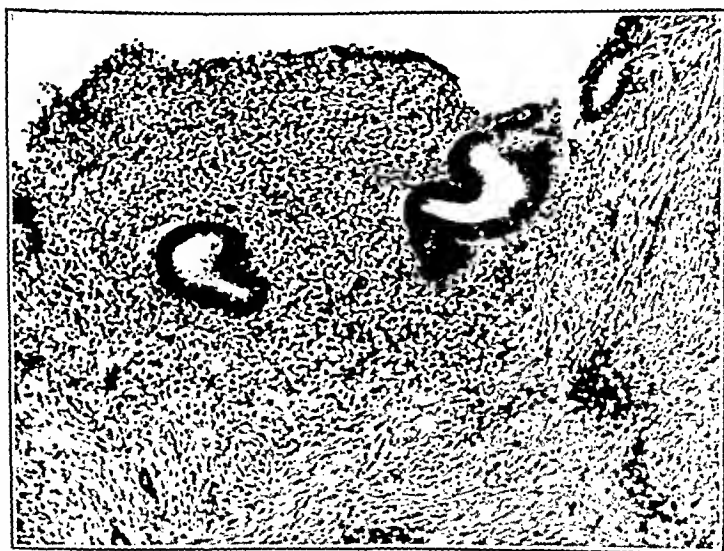


Fig. 5.—Section of tumor found in Case 3; endometrial glands are surrounded by a great number of stroma cells (x105).

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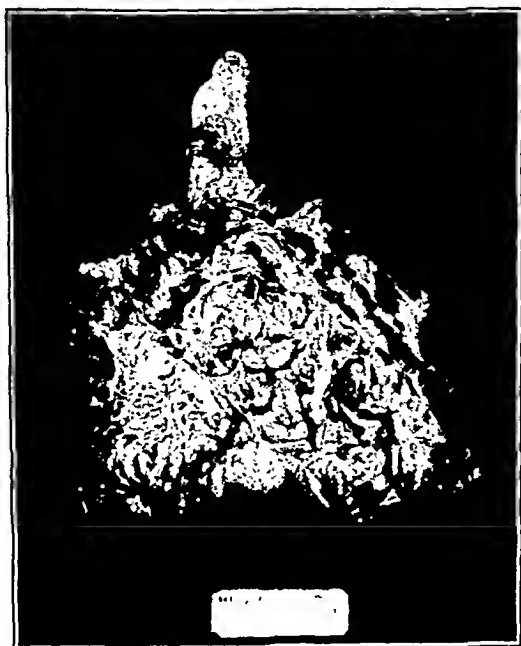


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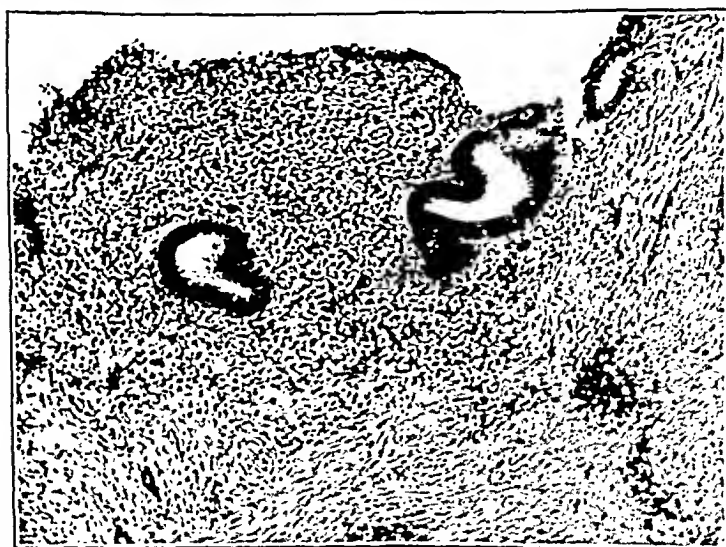


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Microscopic examination of the inguinal tumor (Fig. 1) revealed the typical picture of adenomyoma.

CASE 2.—A married woman, aged forty-four years, who was the mother of two living children, complained of a lump in the right inguinal region. Eighteen years before her registration at the clinic, a right herniorrhaphy had been performed. The incision had drained for four months but the character of the drainage was not stated. Menses had always been regular.

Soreness and pain had been present in the right inguinal region for six months, and four months before she came to the clinic she had noticed the lump. The symptoms had been more pronounced during menstruation.

A firm, movable, tender nodule was palpable just below the old herniorrhaphy scar over the spine of the pubis. Although the patient said that she had had a left inguinal hernia, this could not be demonstrated.

At operation the mass was found to be connected with the terminal portion of the round ligament; it was removed together with a portion of the ligament. There were bilateral indirect inguinal hernias. These were repaired.

The tumor measured 5 by 4 by 2.5 cm., and 2.5 cm. of the round ligament was attached to it. The tumor was firm in consistence and completely covered by fatty tissue. The cut surface was dark brown in color and was reticulated. The trabeculae were grayish in color and between them there were many small cysts filled with a dark fluid (Fig. 2).

The microscopic appearance was that of an adenomyoma (Fig. 3).

CASE 3.—A married woman, aged thirty-nine years, had undergone an appendectomy seventeen years before she came to the clinic. This had been followed by phlebitis in the right thigh. Two years prior to her registration at the clinic she

had had a postpartum infection following the delivery of a stillborn child. Menses had been regular and the interval between the menstrual periods had been twenty-eight days.

The patient complained of a pain over the right lower quadrant of the abdomen following each menstrual period; this symptom had first been noted just after the

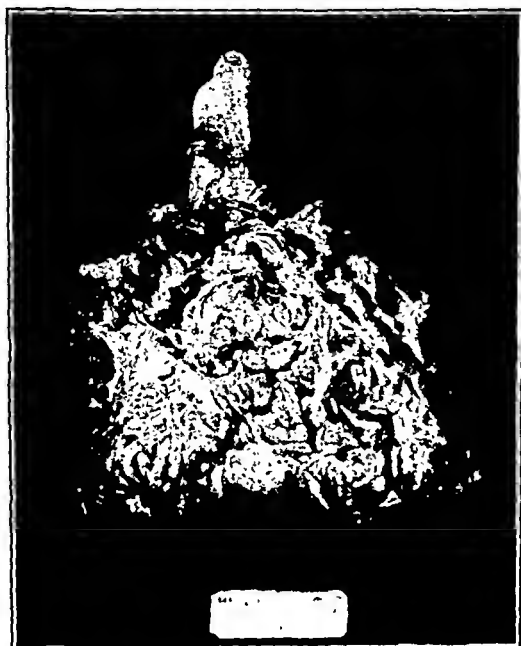


Fig. 4.—Tumor found in Case 3; round ligament is attached to upper part of the mass; tags of fat, fibrous septa, and even small cysts are visible.

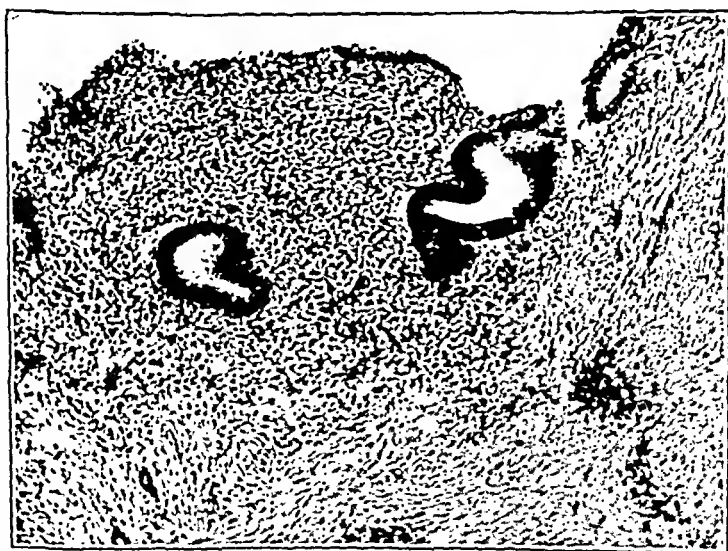


Fig. 5.—Section of tumor found in Case 3; endometrial glands are surrounded by a great number of stroma cells (x105).

delivery of the stillborn child. The pain had been dull and aching in character; it never had been very severe, but it often had persisted for ten or fifteen days after the menstrual period. At times there had been a real sharp pain over the abdomen and the pain occasionally had extended into the right hip and thigh.

Physical examination revealed a healthy appearing woman. There was a healed scar over McBurney's point and tenderness was present over the right lower abdominal quadrant. In the lower part of the right inguinal region there was a firm, tender, fairly well fixed, irreducible mass which measured 3 by 4 cm. On further questioning the patient said this lump had never been reducible, did not increase in size on coughing or straining, and the pain was not made worse when she stood up. The pelvic outlet was relaxed; the anterior lip of the uterine cervix was eroded; the uterus was in the anterior position and freely movable. No adnexal masses were palpated.

Operation was performed by C. W. Mayo. He noted that the mass was hard and scarred as though there had been inflammation in it. The mass, with a portion of the round ligament, was excised and the wound was closed as it is in a hernial repair.

The tumor measured 6 by 4 by 3 cm.; 2.5 cm. of round ligament was attached to it. The mass was firm in consistency and covered by tags of fat. On cross-section (Fig. 4) it was a dark mahogany color except for the grayish fibrous bands which traversed it. There were innumerable small cysts which, when ruptured, exuded a thin, dark, syrupy serum.

Microscopic examination (Fig. 5) confirmed the diagnosis of adenomyoma.

#### COMMENT

Adenomyomas may occur at any point in the round ligament from its uterine attachment to its termination in the labium majus. Loekyer<sup>22</sup> was of the opinion that they are three times as common in the extra-peritoneal portion of the ligament as they are in the intraperitoneal portion, and Cullen<sup>10</sup> said that they are usually found near the external inguinal ring. The intraabdominal tumors cause no characteristic symptoms or signs and the diagnosis of adenomyoma in this situation can rarely be made clinically.

The frequency with which hernia is associated with inguinal adenomyoma is striking. In 1916 Cullen reported a case in which an adenomyoma of the round ligament was associated with incarcerated omentum in an inguinal hernia. He said that to the best of his knowledge it was the first case of that nature reported, and I have found none which antedates Cullen's. Of 8 cases of inguinal endometriosis which Harbitz reported, inguinal hernia was present in 3, femoral hernia was present in 1, and in 1 there was a funnel-shaped distention of peritoneum. Christopher, Palmer, Sampson<sup>33</sup> and others have reported cases in which inguinal endometriosis was associated with hernia. Bilateral hernias were present in Case 2 in the present report.

The diagnosis of a typical adenomyoma of the inguinal region should offer no difficulty. The presence of a more or less fixed, irreducible swelling in a woman in the childbearing age, which is more prominent and more painful during each menstrual period, or is associated with discomfort which is more pronounced following the menstrual period,

should lead one to suspect the true nature of the tumor. Occasionally, the mass will have been present for many years. In the case reported by Blumer, the patient had noticed the mass twenty-three years before she consulted a physician, and in the case reported by Christopher the patient had endured pain for more than fifteen years. One of the patients in the present series of cases had not experienced any pain which was referable to the tumor, and in one case pain had been present for only six months and the presence of the tumor had been noticed only four months before the patient came to the clinic. In one of the cases reported by Palmer<sup>28</sup> the patient complained of an "abscess" of the vulva which had been discharging for two years and which had caused throbbing pain during menstruation. In the case reported by Shaw, the inguinal mass had been mistaken for a broken-down lymph node and had been incised. A sinus had developed and blood had been discharged at each menstrual period.

As far as I am aware, this sympathetic relationship to menstruation produces the only pathognomonic signs and symptoms, although the presence of adenomyoma might be strongly suspected when an inguinal mass exists concomitantly with pelvic adenomyoma. It was pointed out by Beck that the symptoms produced by herniation of an ovary into the canal of Nuck, which first was recognized by Soranus, of Ephesus, might simulate those of inguinal adenomyoma. If inguinal adenomyoma has remained asymptomatic, the diagnosis will probably be made only by the pathologist.

It is to be noted that the round ligaments were involved in the first case reported by Cullen. In reporting a case in 1898, Blumer said that he could find no attachment of the tumor to the round ligament but, he wrote: "the histological structures and situation almost preclude its origin from anything but the round ligament." Harbitz recently said that the finding of smooth muscle fibers in endometrium-like tissue in the inguinal region is usually taken as an indication of connection with the round ligament. In two of the cases reported in the present paper the tumor was attached to the round ligament but in the third case a definite connection could not be demonstrated.

Inguinal adenomyomas are usually of small size; they rarely measure more than 5 to 6 cm. in diameter. At operation the surgeon may be impressed with the inflammatory reaction around the tumor. There is an abundance of adipose tissue surrounding each tumor and a portion of round ligament may be attached to the tumor. When the tumor is sectioned, it is found to be dense and tough and its substance is traversed by a network of interlacing bands of fibers, which are grayish in color and glistening in the fresh specimen. Interspersed between these bands of fibers are small chocolate-colored vesicles which, when ruptured, release a dark, syrupy fluid. The largest cyst in any of these cases was 8 mm. in diameter, but most of the cysts measured about 1 mm.

On microscopic examination the tumor is found to be composed of fibers of connective tissue and smooth muscle which have no definite arrangement. Van Gieson's method of staining revealed a predominance of connective tissue in two specimens, while in a third specimen smooth muscle fibers predominated. Several areas of adipose tissue were scattered throughout the tumor and blood vessels were very numerous. Glands of various sizes and shapes were found in all parts of the tumor. These glands, which were called miniature uterine cavities by Cullen, were lined by columnar epithelium and most of them were surrounded by a stroma similar to that of the uterine mucosa, but a few rested directly on the muscle or connective tissue fibers. Large phagocytic cells containing blood pigment were present in abundance.

Robert Meyer, according to Graves, expressed his belief that the appearance of smooth muscle fibers, except in rare embryonic tumors, is due to irritating hyperplasia produced in the surrounding tissues. Graves subscribed to this teaching and said that the term adenomyoma is, therefore, a misnomer. The paucity of smooth muscle fibers in the specimens obtained in the present series of cases might lend some support to this theory.

Cullen<sup>8</sup> was the first to draw attention to the clinical analogy between adenomyoma and the menstrual endometrium, and in 1908 he reported a case in which there was a tubal pregnancy in the left fallopian tube and diffuse uterine adenomyoma in the right horn of the uterus. The stroma cells around the adenomyomatous region had undergone the typical reaction of pregnancy. Palmer reported a case in which he found a ruptured tubal pregnancy and a nodule in the mons veneris on the right side, which extended upward into the inguinal canal. The microscopic picture of adenomyoma was altered by the tubal pregnancy.

The origin of inguinal adenomyoma is as debatable today as it was when first described by Cullen, and many theories have been advanced. Cullen has always believed that these tumors are derived from misplaced portions of Müller's duct. As evidence of this he drew attention to the similarity of the glands in adenomyoma to the normal uterine glands and to the fact that the glands are surrounded by stroma like that found in normal uterine mucosa. The sympathetic relationship of the misplaced glands with the menstrual periods, or their response to the hormones which govern the activity of the uterine endometrium, is well known and would indicate a similar origin of them and the uterine glands. The occurrence of a pregnancy in adenomyoma has even been described.<sup>13</sup> As late as 1925, Cullen<sup>11</sup> again emphasized his conviction that typical adenomyomas originate from the müllerian duct and said that adenomyoma of the round ligament must be considered as an embryonic inclusion since it would be impossible to explain it

by transplantation. Ewing was of the opinion that "it would be wise to assume that in all probability they are of congenital and not of the acquired type."

Von Recklinghausen said that adenomyomas are of wolffian origin, as previously mentioned. This opinion was based on the supposed close analogy between elements of the wolffian duct and the glandular structures of the tumors. This theory has gradually lost ground and today it has few supporters.

The implantation theory of the origin of aberrant endometrium-like tissue, which has created tremendous interest and debate, was advanced by Sampson<sup>32</sup> in 1921 in an article entitled "Perforating Hemorrhagic (Chocolate) Cysts of the Ovary." According to this view, fragments of the uterine mucosa migrate through the fallopian tubes during menstruation and lodge on the ovary. There they are nurtured and chocolate cysts eventually are formed. With the increase in tension due to the accumulation of blood in the cyst, perforation may occur and fresh implants are scattered over the pelvic peritoneum and adjacent structures with resulting inflammation and the formation of new cysts. Sampson<sup>33</sup> said that there may be a direct extension along the round ligament, from these implants, or from peritoneal endometriosis situated about the internal inguinal ring, or there might be implantations in a hernial sac. Another possibility, which was advanced by Halban and supported by Sampson,<sup>33</sup> is that of metastasis through the lymphatics or veins accompanying the round ligament. Sampson<sup>34</sup> has expressed the belief that fragments of endometrial tissue are occasionally disseminated into the venous circulation during menstruation and he said that metastatic or embolic endometriosis may arise from this source.

The following objections to the implantation theory have been most clearly and lucidly voiced by Novak. He has never seen menstrual blood escaping from the tubal ostia, and in thousands of cases in which operation was performed just after menstruation, blood was not found in the peritoneal cavity, and there was no evidence of peritoneal irritation as is usually produced by blood. Regurgitation is too infrequent to explain a condition as common as aberrant endometrium-like tissue. The action of the cilia of the tubal epithelium is toward the uterus and would probably not allow retrograde transplantation of fragments of endometrium. The viability of cast-off endometrium is highly improbable, and the delicate peritoneum would offer a more inviting field than the dense and avascular albuginea of the ovary.

The serosal theory of the origin of aberrant endometrium-like tissue is associated with the names of Iwanoff and Meyer, the former having shown that ingrowing processes of epithelium derived from the peritoneum may give rise to the cystic spaces found in some fibromyomas, and Meyer having shown that epithelial heterotopy can occur in the

serosa. Novak supported the ectopic differentiation of ectopic epithelium as a source of aberrant endometrium. The ectopic epithelium of the urogenital folds gives rise to the germinal epithelium of ovary, the follicular epithelium, and the lining of the müllerian ducts. Since tissues derived from the same embryonic mother epithelium are similar, it is "not surprising that either peritoneum or germinal epithelium may at times show endometrial transformation." The endometrium-like tissue which appears in the inguinal region or in the vulva may arise from the remains of the processus vaginalis which has become activated.

The frequency with which adenomyomas are encountered, and their surgical importance, together with the mystery surrounding their origin, warrant a sustained interest in this subject.

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## REMOVAL OF THE UPPER JAW AN HISTORICAL OPERATION

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THE United States was in the throes of a financial crisis in 1893, a crisis which might easily have ended in a panic causing a world-wide catastrophe. It was a question whether or not the country should go off the gold standard, and there were fierce arguments on both sides. It was said openly that Mr. Cleveland was about all that stood between the people and absolute disaster, and his death would be a great calamity. The words were spoken in innocence, but only three persons knew how near these words were to the truth.

Vague rumors were circulated that the President was not as well as he should be, and that he had gone from Washington into sudden retirement to his country house at Gray Gables on Buzzards Bay, Massachusetts. Inquiries were made, and Colonel Lamont, Secretary of War and Cleveland's most intimate friend, telegraphed to Washington: "The President is laid up with rheumatism in his knee and foot, but will be out in a day or two. No occasion for any uneasiness." This statement, however, did not satisfy the press, so Colonel Lamont invited the representatives of the chief newspapers to meet him that he might give full explanation of everything. He asked that they should say nothing until they had seen him and purposely fixed a late hour when the evening editions were already off the press.

The reporters found headquarters at an hotel near the railway station at Buzzard's Bay. At the appointed hour, they walked in a body across the old railway bridge down to Gray Gables, a mile and a half away. Colonel Lamont met them at an old barn, about 200 yards from the house. He greeted the men cordially, and told them it was really very foolish to make such a stir over a matter which was essentially trivial. The President had suffered from an attack of rheumatism to which he was occasionally subject, and had made a prolonged journey on Mr. Benediet's yacht for some dentistry. The President, being very busy, disliked having a dentist over him and consequently had allowed his dental work to become so badly neglected that he finally felt compelled to go on the yacht; there he would be cool and comfortable while the dentist could do a thorough job of fixing his teeth. The newspapermen inquired the name of the dentist, what had to be done, and other minor details to which Lamont replied that they were too trivial to talk about.

The reporters walked back to the hotel arguing briskly. Half of them did not believe what they had been told; the other half were more credulous. They reached an agreement, however, that they would stand together on whatever story they should send out, and then went into conference at the hotel to decide what their story should be. The next day, without a dissenting voice, the newspapers, including the press associations, gave to the country a reassuring version of the



Fig. 1.—Grover Cleveland. (After Nevins Allan: Grover Cleveland, New York, 1932, Dodd, Mead & Company, Inc., p. 304.)

case. At 6 o'clock on Friday evening, June 30, an extra session of Congress was summoned to meet on August 7.

When Congress met in special session on August 7, Mr. Cleveland's message urged the absolute repeal of the Sherman Act without any substitute and without any compromise. On August 11 Mr. Cleveland returned to Gray Gables, and while there he heard that the House had passed the repeal on August 28 by a vote of 239 to 101; on October 30 the repeal was passed by the Senate.

The inner history was revealed many years afterwards by Dr. W. W. Keen, the doyen of American Surgery. Writing in 1917, he says,

"On Sunday, June 18, 1893, Dr. R. M. O'Reilly, the official medical attendant on officers of the government in Washington, examined a rough place on the roof of Mr. Cleveland's mouth. He found an ulcer as large as a quarter of a dollar, extending from the molar teeth to within one-third of an inch of the middle line encroaching slightly on

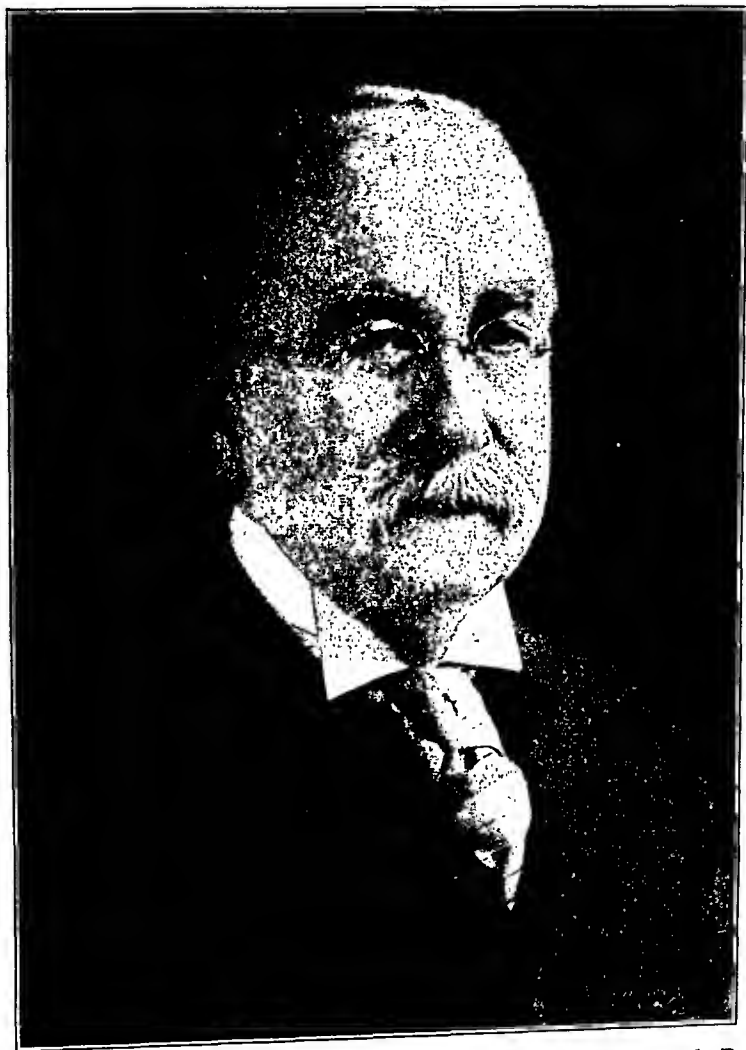


Fig. 2.—William Williams Keen, M.D., Sc.D., Ph.D., LL.D. (From Am. Med., December, 1921.)

the soft palate, and some diseased bone. The pathologist at the army medical museum reported that the tissue sent to him was strongly suggestive of malignancy. Dr. Joseph D. Bryant, an intimate friend and the usual medical attendant of the President, confirmed the diagnosis and recommended immediate removal. Mr. Cleveland consented to an

operation provided that a time and place was chosen where publicity could be avoided, and decided that July 1 was the earliest suitable date for himself. Colonel Lamont was told of the decision and it was agreed that to secure secrecy the operation should be done on the



Fig. 3.—Joseph D. Bryant, M.D. (From Surg., Gynec. & Obst., February, 1908.)

'Oneida,' Commodore Benedict's yacht, and that the President should return to Washington on August 7.'

Dr. Keen was called in consultation, and Dr. Bryant met him at a quarter past three on the deck of the Fall River boat which was then deserted as the sailing did not take place until six o'clock. Here without interruption the necessary plans were arranged. The living

rooms on the "Oneida" were prepared and disinfected; an operating table and all the necessary instruments, drugs, dressings, etc., were sent on board. Dr. Ferdinand Hasbrouek, a dentist accustomed to giving nitrous oxide, was asked to assist.

Dr. Keen arrived in New York on June 30, went to Pier A and was taken over to the yacht which was lying at anchor at a considerable distance from the battery. Dr. E. G. Janeway of New York, Dr. O'Reilly, Dr. John F. Erdmann, Dr. Bryant's assistant, and Dr. Hasbrouek had also gone secretly to the yacht. The President, Dr. Bryant, and Secretary Lamont arrived later from Washington and drove openly to Pier A, whence they were taken to the yacht.

On arriving at the yacht the President lighted a cigar and sat talking on deck until nearly midnight. He passed a good night sleeping well without a draught, and before he dressed the next morning, Dr. Janeway made a careful examination of his chest. Nothing was found to be wrong; there was, however, some evidence of arteriosclerosis and his kidneys were believed to be almost normal. Dr. Keen also examined the President and was told that the rough place in his mouth was not there on March 4, but had been first noticed six or eight weeks before the first of July. There were no perceptibly enlarged glands, but Dr. Keen had no doubt that the growth was unquestionably malignant. The patient's mouth was repeatedly cleansed and disinfected in the course of the morning.

The anesthetic caused some anxiety for the President was fifty-six years of age, very corpulent with a short, thick neck, and tired out by four months of exacting labor. The whole matter was considered carefully, and it was decided that Dr. Hasbrouek should give nitrous oxide first, and ether later if necessary.

The operation was performed on July 1 while the yacht was going up the East River at half speed. Commodore Benedict and Secretary Lamont remained on deck while the operation was being performed in the cabin. Dr. Hasbrouek first extracted the two upper left bicuspid teeth under nitrous oxide, and Dr. Bryant then made the necessary incisions in the roof of the mouth also under nitrous oxide. Ether was given by Dr. O'Reilly at 1:14 p.m. while Dr. Janeway kept a close watch upon the patient's pulse and general condition; Dr. Keen and Dr. Erdmann acted as assistants to Dr. Bryant.

The entire left upper jaw was removed from the first bicuspid to just beyond the last molar and close to the middle line. The floor of the orbit was left and a small part of the soft palate was cut away. The antrum was filled with a gelatinous mass which Professor W. W. Welch afterward reported as sarcomatous. The entire operation was done within the mouth without any external incision. The absence of an external scar, or of any displacement of the eye together with the

preservation of the normal voice aided greatly in keeping the operation a secret. The bleeding was not severe, only one artery had to be tied, and the patient did not lose more than six ounces of blood. The operation was finished by 1:55 p.m., and an hour later a hypodermic of one-sixth grain of morphine was given which did not need to be repeated. The patient made a good recovery. He was up and about on July 3, and on July 5 he walked from the launch to his home at Gray Gables with little apparent effort. A small secondary operation was performed on July 17 when the galvanocautery was used to remove a small portion of suspicious looking tissue; a prosthetic appliance was supplied by the dentist, and the patient was able to go about his ordinary duties. Mr. Cleveland died June 24, 1908, fifteen years after the operation, without any recurrence of the growth.\*

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\*The information is taken from "The Surgical Operations on President Cleveland in 1893" by William W. Keen, M.D., LL.D., Philadelphia, Pa. George W. Jacobs and Co., 1917, pp. 52.

## Editorials

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### Peptic Ulceration

ULCERATION of the stomach and duodenum, although relatively easily treated by conservative measures, still represents a therapeutic problem, because of the great tendency toward recurrence. As is well known, seasonal recurrence of peptic ulceration is the rule, and many patients have been repeatedly cured of a gastroduodenal ulceration only to have the ulcerative process return at some subsequent date.

Many theories concerning the causation of chronic ulceration of the stomach and duodenum have been suggested, and in all probability there are several factors which are responsible in individual cases. Because gastroduodenal ulcers usually recur following a satisfactory healing of the ulcerative process, the likelihood of a constitutional predisposition of the ulcer must be considered. At the present time it cannot be definitely stated what the underlying abnormality is which is responsible for the predisposition to ulceration. It may be a sympathico-adrenal hyperirritability, as suggested by Crile; a vagotonia, as suggested by Bergmann; or a peculiar arrangement of the capillary mucosa of the stomach with the formation of large plexuses in the submucosa, as demonstrated by Dusehl, Mueller, and Heimberger. A realization and acceptance of the constitutional predisposition to peptic ulcer in ulcer patients is important from the standpoint of therapeutics, because obviously recurrence of the ulceration is likely when the patient is subjected to the same conditions. This probably accounts for the fact that gastroduodenal ulcers frequently recur under the present methods of therapeutic management and, unless the therapy is changed, recurrence of the gastroduodenal ulcer will continue to be the rule rather than the exception.

If one accepts the constitutional predisposition to ulceration in ulcer patients, how can one account for the healing of an ulcer in such an individual? Undoubtedly the ulcer diathesis alone is not sufficient to produce a mucosal ulceration of the stomach and duodenum. There must be in addition some *other factors* which are "precipitating" ones. Of the precipitating factors, gastric hyperacidity, gastric trauma, and pylorospasm are the most important. Of these three, hyperacidity occupies the first rôle, because as long as these ulcers have been treated, whether conservatively or radically, healing has followed the use of measures which tend to reduce the acidity of the stomach and

duodenum. The control of the precipitating factors, namely, hyperacidity, gastric trauma, and pylorospasm, in an individual with an ulcer diathesis will usually bring about a healing of the ulcerative process. As a matter of fact, only exceptionally is it difficult to secure healing of a peptic ulcer if conservative measures are employed. Too frequently, however, the physician's and patient's attentions are focused on the presenting symptom, the ulcer, and after the ulcer has healed the patient is allowed to revert to his former method of living, which again permits the precipitating etiologic factors to come into play and result in a recurrence of the ulcer. In such instances it is probably just as illogical to direct one's entire attention toward the healing of the ulcer, which is merely a symptom of an underlying constitutional abnormality, as it is to direct one's attention toward the control of the fever in a systemic condition which is associated with pyrexia.

If the conception that the ulcer patient has a constitutional predisposition to gastroduodenal ulceration is correct, it becomes necessary for the therapy of the patient to extend probably throughout his lifetime; and as little can be done as regards the predisposing factors, the treatment should consist of controlling the precipitating factors. This does not mean that a patient is forced to remain on a strict dietary regimen throughout the rest of his life, because, whereas a strict dietary plan may be essential in the presence of acute ulceration, it is certainly not necessary after the ulcer has healed. In such instances the avoidance of those factors which predispose to the precipitating causes is usually all that is necessary for the patient to remain well. As hyperacidity is increased by smoking and the ingestion of alcoholic beverages, it is imperative that the patient with an ulcer diathesis abstain totally from tobacco and alcohol. Because food is an excellent neutralizing agent, such individuals should eat frequently, four to five times a day, for the rest of their lives, never overeating at any time. As gastric trauma is a precipitating factor, the avoidance of rough foods is essential. The observance of such a conservative therapy, namely, the alteration of the life of a patient with an ulcer diathesis, will probably result in a prevention of a recurrence of the ulcer by obviating the precipitating factors in an individual with a constitutional predisposition.

If the above conception of gastroduodenal ulceration is correct, it is improbable that surgical measures for the cure of ulceration per se will be of any value. It is the definite opinion of the author that surgery of peptic ulceration should consist largely, if not entirely, of the treatment of complications and not of the ulceration itself. It is illogical to assume that predisposition to the ulcerative process can be altered by a surgical procedure.



Because of the definite susceptibility of certain portions of the gastrointestinal tract to the peptic digestive activity to the acid gastric chyme, as is demonstrated by the predilection sites of ulceration in the gastroenteric system, it is important that a surgeon avoid those operations which will subject an abnormally susceptible portion of the intestine to the acid gastric chyme. Reference is made particularly to the promiscuous performance of gastroenterostomy, because, as can be shown experimentally and clinically, the susceptibility to peptic digestion increases with the aboral distance from the pylorus. In other words, the jejunal mucosa is more susceptible to the digestive action of the acid gastric chyme than is the duodenal mucosa, and the ileal mucosa is more susceptible than either of them.

Although gastrojejunostomy is the most frequently employed operation in the treatment of gastroduodenal ulceration today, it is in many cases a dangerous procedure because of the likelihood of an ulcer occurring in the jejunal mucosa opposite the gastroenteric stoma. One cannot deny that a gastroenterostomy frequently gives splendid results, and it is the operation of choice in those cases of pyloric occlusion in which, as a result of the long-standing gastric stasis, there has occurred an atrophic gastritis with a hypochlorhydria or an achlorhydria. The emptying of the gastric chyme into the jejunum in such an instance because of the low or absent free hydrochloric acid does not result in an ulceration of the highly susceptible jejunal mucosa. In a patient, however, with a hyperacidity a similar operative procedure is likely to cause a jejunal ulceration. It is for this reason that careful preoperative gastric analyses should be made in all cases of peptic ulceration in which an operative procedure is considered.

Of greatest importance in the treatment of gastroduodenal ulceration is the realization by the physician and the patient that the lesion limited to the stomach or the duodenum is only a part of an underlying constitutional predisposition, and that in order that a satisfactory result can be obtained, it is necessary that the patient change his mode of living in such a way that the precipitating factors which are responsible for the ulceration are obviated. When such plan of treatment is used, undoubtedly the high incidence of recurrence of ulceration can be decreased. In the surgical treatment of complications of peptic ulcer, it is important to avoid those procedures which will subject an abnormally susceptible portion of the intestinal tract to the acid gastric chyme. In a patient with a hyperacidity a gastrojejunostomy should not be done, but preferably a pyloroplasty or gastroduodenostomy, both of which permit the emptying of the acid gastric chyme into a portion of the intestinal tract accustomed to receiving it, i.e., the duodenum. In perforations of a peptic ulcer, simple closure of an ulcer without the performance of a gastroenterostomy should be

done. In cases in which malignant change in the ulcer is suspected, such as calloused ulcer on the lesser curvature which does not respond to conservative therapy and all ulcers on the greater curvature, because many of these are primarily malignant, a subtotal gastrectomy should be performed.

—Alton Ochsner.

### Infections of the "Dangerous Area" of the Face

THE majority of infections of the so-called "dangerous area" of the face are of minor significance. In a small group, fortunately a very small group, the infection is fulminating in character and the fatal outcome is almost predetermined. Between these two extremes, however, lies another group of cases in which an originally insignificant lesion by unwise methods of management and by meddlesome interference is converted into a condition which is always dangerous and which is very frequently fatal. There is no more tragic group of cases in surgery because there is no group of cases in which the lethal issue is so utterly unnecessary.

Any lesion in the "dangerous area" of the face has the gravest potentialities for harm. The surgeon who recognizes these potentialities and who impresses them upon his patients is no alarmist but a truly conservative practitioner. Yet all too often he fails to utter the warning. The regrettable truth is that he does not himself recognize the risk of infection in this area because he does not know, or does not take the trouble to recall, the anatomic and physiologic circumstances which prevail.

The skin about the mouth and lips is thickly interwoven with underlying muscle fibers, blood vessels, and lymphatics, which are here embedded in an unusually small amount of connective tissue. The distribution of the venous supply provides what amounts to a direct connection between the veins of the lip and the cavernous sinus in the anterior of the cranium; and the veins, furthermore, are lacking in valves and possess relatively rigid walls. The stage is set anatomically for a rapid spread of infection, and on the physiologic side the picture is equally unpropitious. The first principle of the limitation of infection is the limitation of motion in the affected area, and the environment here militates against it. Eating, drinking, smiling, laughing, talking, crying, even thought and emotion, result in changes of facial expression. Motion may be expressly prohibited, but the prohibition is almost impossible to obey absolutely, and the delirious and comatose states which ensue early in the disease are other factors against its fulfillment.

To these inevitable and unpreventable circumstances is added an external factor, trauma, which, although entirely preventable, is present in at least 90 per cent—some authorities say 100 per cent—of all

serious cases. It is usually introduced by the patient, but in too large a number of cases it is increased by the physician, if the initial responsibility be not actually his. His instinct, like the patient's, is to do something about it. Once manipulation is undertaken, a superficial lesion promptly becomes potentially if not actually serious. Rarely is pus obtained in any amount. Usually blood or bloody serum is forced into the surrounding tissues, increasing the tension of the parts and furnishing an excellent culture medium for the bacteria already present. The wall of leucocytes, upon the integrity of which the limitation of the infection depends, is broken down. The connective tissue about the mouth accommodates itself very poorly to infection, which is carried onward without obstruction by the rich venous supply, the process being accelerated by the constant motion of the affected parts and the absence of valves in the facial vein. One step rapidly succeeds another. Thrombophlebitis passes over into a thrombosis of the vital centers. Unilateral disease tends to become bilateral early because of the close communication between the cavernous sinuses by interlocking venous channels. The final stages of meningitis and septicemia are not long delayed, and metastatic foci develop elsewhere in the body if the patient should live long enough; he usually does not.

The dramatic progression of pathologic events is paralleled clinically. Beginning as an insignificant carbuncle, furuncle, or boil, with slight or absent local symptoms, the initial lesion rapidly exhibits marked swelling, reddening, induration, and edema of the parts. The patient suffers excruciating pain. Chills occur, the fever mounts to  $107^{\circ}$  or  $108^{\circ}$  F., and higher, and the pulse rate is correspondingly accelerated. The swelling becomes more extensive, involving the eyelid, closing the eye, producing exophthalmos, and causing the characteristic "butterfly" discoloration of the tissues of the forehead. The patient, who is extremely toxic, is comatose or wildly delirious. The course of the whole illness is incredibly swift, and when the stage just described has been reached, the fatal outcome is not long delayed.

Diagnosis offers no problems, but treatment offers many. Most of the therapeutic suggestions may be dismissed without very much consideration. These include local application of various bright-colored antiseptics; cauterization by phenol or the electric cautery, or the injection of carbolic acid; eirenminjection of the lesion by the patient's own blood; Bier suction; and the use of Bier's constricting band around the neck. Most of these methods are meddlesome and have inherent in them the element of trauma which must, at all costs, be avoided. More rational is the suggestion that any lesion in this area, immediately on its development, should be splinted with adhesive tape, to secure immobility of the affected area.

The general opinion today in well-informed surgical circles is that the less done locally the better, regardless of the stage of the process.

If the patient keeps his hands off the initial lesion, and if the physician follows suit, the majority of such infections will die a-borning. The local application of alcohol or some similar drying agent may furnish to both parties the mental relief of some sort of action, but manipulation must be strictly avoided. Both for the initial lesion and for the lesion in more advanced stages, x-ray therapy seems to be developing a clear field of usefulness. Many cases are on record in which this method has apparently aborted mild infections and controlled more severe ones, the favorable action, according to a recent editorial in the *Journal of the American Medical Association* (109: 278-279, 1937), being due to the breaking down of certain radiosensitive cells and the consequent liberation of powerful antitoxic substances.

Rest in bed, preferably in the hospital, is obligatory for any but the simplest case. Speech is strictly forbidden, as is any other action requiring motion of the lips. Only liquid nourishment is given, and it is usually administered by nasal tube. Opiates and sedatives are employed as necessary. Local measures are limited to the use of compresses, which must be small and light and which must be kept constantly moist, preferably by the use of a medicine dropper. Tap water, or some saline solution, is entirely satisfactory, and it is essential that the temperature be moderate; the patient's pain is often so severe that he may be burned without comprehending what is happening. Incision is reserved strictly for the time when localization shall have occurred. The routine use of these precautions often suggests to the patient much ado about nothing, but the physician is entirely justified in insisting upon them. For one thing, when they are employed early enough, they are practically always effective. For another, the end results of this condition are serious enough to warrant any amount of care in aborting them.

Even when thrombophlebitis has frankly occurred, the general opinion is that conservative measures are still best. In spite of the successful cases on record, most surgeons of experience regard ligation of the angular vein as of dubious value. The anatomic circumstances are against success because of the rich venous anastomosis in this area. If ligation is done late, infection is likely to have extended beyond the point at which the ligature is applied, while there is the additional danger of loosening the clot by the surgical manipulation, however carefully it is done.

Few patients survive when the infection has reached the cavernous sinus, and most surgeons agree that thrombosis in this region can scarcely be considered a surgical complication, if for no other reason than that meningitis develops so promptly after it has occurred. It has been estimated that while only 7 per cent of such patients recover without surgery, less than 7 per cent recover with it.<sup>1</sup> The management of the terminal septicemia and meningitis offers no problems which are not presented at other times, although the very occasional case in which

serious cases. It is usually introduced by the patient, but in too large a number of cases it is increased by the physician, if the initial responsibility be not actually his. His instinct, like the patient's, is to do something about it. Once manipulation is undertaken, a superficial lesion promptly becomes potentially if not actually serious. Rarely is pus obtained in any amount. Usually blood or bloody serum is forced into the surrounding tissues, increasing the tension of the parts and furnishing an excellent culture medium for the bacteria already present. The wall of leucocytes, upon the integrity of which the limitation of the infection depends, is broken down. The connective tissue about the mouth accommodates itself very poorly to infection, which is carried onward without obstruction by the rich venous supply, the process being accelerated by the constant motion of the affected parts and the absence of valves in the facial vein. One step rapidly succeeds another. Thrombophlebitis passes over into a thrombosis of the vital centers. Unilateral disease tends to become bilateral early because of the close communication between the cavernous sinuses by interlocking venous channels. The final stages of meningitis and septicemia are not long delayed, and metastatic foci develop elsewhere in the body if the patient should live long enough; he usually does not.

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# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## HYPOGLYCEMIA

NATHAN A. WOMACK, M.D., ST. LOUIS, MO.

*(From the Department of Surgery, Washington University School of Medicine, and Barnes Hospital)*

ONLY a few years have elapsed since Wilder<sup>1</sup> and his coworkers confirmed Seale Harris<sup>2</sup> conception of a clinical entity of hyperinsulinism. Their demonstration of the presence of insulin in the metastases of a tumor arising in the pancreas, the clinical picture of which resembled in every respect the syndrome of overdosage from insulin, marked one of the important mileposts in the progress of endocrinology. Shortly after the appearance of this observation, other examples, differing somewhat in type, began to appear, including several reports from this institution.<sup>3</sup> Very rapidly a considerable amount of clinical and experimental data related to the subject has been amassed. So extensive is the literature that a careful detailed review of it would require a monograph of considerable size. Such a study is hardly necessary in view of the fact that already several adequate papers reviewing the earlier literature have appeared. In America, those of Harris<sup>4</sup> and Whipple and Frantz<sup>5</sup> are outstanding. Wauchope<sup>6</sup> in England, Sigwald<sup>7</sup> in France, and Joseph Wilder<sup>8</sup> in Germany have contributed extensive bibliographies. In this review, so far as possible, I shall stress those contributions that have appeared since the last of the above reviews, referring only briefly, wherever necessary, to earlier studies.

It has become more and more apparent that our conception of hypoglycemia must be exactly opposite from that of diabetes mellitus. Those factors at play in the elevation of the level of sugar in the blood can likewise cause the lowering of sugar in the blood. Unfortunately, this mechanism is at the present time poorly understood in many of its aspects, just as is the study of carbohydrate metabolism, with which it is intimately concerned. Harris originally considered hypoglycemia a result of an excessive secretion of insulin into the blood stream, just as diabetes mellitus had been considered the result of a deficient secretion of insulin. Such a conception was only logical. Since the original observations of Minkowski that total removal of the pancreas was associated with glycosuria, attention was almost completely focused on the pancreas. It was soon established that in external pancreatic fistulas this glycosuria did not occur, nor was it present when the entire pancreas was removed

the intravenous use of staphylolysate has been successful suggests a further trial of this agent. Prontosil has not been used for a sufficiently long period of time to permit accurate generalizations concerning it.

Obviously, infections of the "dangerous area" of the face, although infrequent in their serious manifestations, are always potentially highly dangerous and should be treated with the greatest fear and respect, no matter how early they are seen and no matter how trifling they may seem. With the proper prophylaxis, and particularly with the strict elimination of any sort of trauma, the majority will terminate as innocuously as they began. But their harmlessness is dependent upon the self-restraint of the patient who exhibits the lesion and the physician who treats it. In this condition procrastination for once reaps shining rewards and zeal and promptness are attended by fearful consequences. Surgical nihilism is a plan that is generally distasteful to patient and physician alike, but this is one disease in which it is the only type of therapy not attended by a tragic death rate. Walton Martin, who wrote the classical paper on this subject,<sup>2</sup> said almost the last word upon it when he pointed out that the application of any other method will "during a long lifetime lead to an astonishing mortality."

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—Urban Maes, M.D.

New Orleans, La.

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and a small portion of it transplanted. Further evidence of the endocrine nature of this secretion was found when it was noted that there was hyalinization of the islets of Langerhans in occasional patients dying of diabetes mellitus, that these islets did not atrophy when the pancreatic ducts were ligated, and that the beta cells of these islets seemed to be the structures most concerned in the elaboration of this secretion. This conception of the relation of the pancreas to carbohydrate metabolism reached its culmination when Banting and Best were able to produce an active extract that would lower the level of sugar in the blood. Apparently the production of insulin is a unique function of the islets, although other substances have been reported to lower the blood sugar level.<sup>9, 10</sup> It is quite possible that many substances having a hypoglycemic action in the blood stream do so indirectly through their effect on organs intimately concerned in carbohydrate metabolism. Acetylcholine,<sup>11</sup> for example, lowers the blood sugar level either through its action on the vagus or by direct inhibition of glycogenolysis. The hypoglycemic action of insulin is generally constant in a controlled experiment, while the level at which hypoglycemic symptoms occur often varies quite markedly.<sup>12-15</sup>

The association of clinical hypoglycemia with an excessive production of insulin is a rational one and this conception was soon verified by the demonstration of a carcinoma having its origin in the islet tissue with metastases to the liver from which insulin could be extracted.<sup>16</sup> Following this, Rosecoe Graham excised the first localized islet-cell adenoma with cure of the hypoglycemic state.<sup>17</sup> Shortly before this, however, Finney had operated upon a patient and no tumor had been found.<sup>18</sup> For the first time we were thus confronted with the fact that hypoglycemia may be present with no apparent lesion in the pancreas, just as diabetes mellitus often has been found present with no morphologic evidence of insulin insufficiency. In order to understand how this may occur, it will be necessary to review briefly the action of some of the other organs in the maintenance of normal blood sugar level.

#### MAINTENANCE OF BLOOD SUGAR LEVEL

Carbohydrate ingestion does not play as important a part in the maintenance of the level of blood sugar in the normal animal as was once thought. While in prolonged carbohydrate feeding there is an initial rise in blood sugar, this generally returns to normal and remains so.<sup>19, 20</sup> The reverse is true in prolonged fasting, where even an increase in the size and number of the islets has been noted.<sup>21</sup> It must be constantly borne in mind that the blood sugar level will vary in different individuals just as it will vary in the same individual even under basal conditions.

Mollerstrom<sup>22</sup> has recently enlarged upon Forsgren's conception of the rhythmic functioning of the liver with its alternation in glycogen

production and bile secretion. During glycogen production there is a tendency toward carbohydrate retention in the body with a lowering of blood sugar. The reverse holds true during bile secretion. He finds that this endogenous periodicity varies not only in different individuals but likewise in the same individual.

The exact action of the liver in maintaining homeostasis is still poorly understood. The conception of Soskin and his coworkers<sup>23-27</sup> is interesting. In their study concerning the utilization of carbohydrates in totally depancreatized dogs, they found no evidence of impairment of the ability to oxidize carbohydrates. They were able to obtain normal glucose tolerance curves in animals in which the presence of insulin had been completely excluded, a constant blood sugar level being maintained artificially. They are of the opinion that the normal glucose tolerance curve depends upon the response of the liver to exogenous sugar, the organ decreasing its supply to the blood stream in the presence of such an exogenous influx. The action of insulin is to determine the threshold at which this homeostatic reaction comes into play.

While the exact mechanism employed by the liver in its function is still under discussion, the fact that it plays an important rôle in the maintenance of blood sugar levels has been recognized since the days of Claude Bernard. The studies of Mann and Magath<sup>28, 29</sup> on the effects of complete and partial removal of the liver have been of the greatest importance. Although they have noted that if only 15 per cent of the liver is present there is only slight change in blood sugar levels, reports of the experimental production of hypoglycemia by the action of various toxins upon the liver are common.<sup>30-35</sup>

Of striking importance in the maintenance of normal blood sugar level is the anterior lobe of the hypophysis. The fact that the hypophysis was concerned in some way has been recognized for a long time, and as early as 1912 Cushing reported a hypophyseal tumor associated with hypoglycemia. Because of the fact that the hypophysis is apparently an activator for so many of the endocrine glands and that these glands tend to atrophy both anatomically and functionally when the anterior lobe is removed, pure experiments were difficult to obtain until active extracts of these other glands were available. During the past few years considerable information on this subject has accumulated, especially from the laboratory of Hanssaw and his coworkers.<sup>36</sup> When the hypophysis is removed, practically all species of animals present a marked fall in blood sugar on fasting as well as an extreme sensitivity toward insulin. This is not only true of the toad, dog, and cat but also of the Rhesus monkey as well.<sup>37</sup> In an animal made completely diabetic by total removal of the pancreas, hypophysectomy alters markedly the classical features of the diabetes. The animal survives a much longer period; glycosuria may disappear completely and the blood sugar approaches normal. In the fasting animal hypoglycemia is frequently noted; there is a decrease in nitrogen

and a small portion of it transplanted. Further evidence of the endocrine nature of this secretion was found when it was noted that there was hyalinization of the islets of Langerhans in occasional patients dying of diabetes mellitus, that these islets did not atrophy when the pancreatic ducts were ligated, and that the beta cells of these islets seemed to be the structures most concerned in the elaboration of this secretion. This conception of the relation of the pancreas to carbohydrate metabolism reached its culmination when Banting and Best were able to produce an active extract that would lower the level of sugar in the blood. Apparently the production of insulin is a unique function of the islets, although other substances have been reported to lower the blood sugar level.<sup>9, 10</sup> It is quite possible that many substances having a hypoglycemic action in the blood stream do so indirectly through their effect on organs intimately concerned in carbohydrate metabolism. Acetylcholine,<sup>11</sup> for example, lowers the blood sugar level either through its action on the vagus or by direct inhibition of glycogenolysis. The hypoglycemic action of insulin is generally constant in a controlled experiment, while the level at which hypoglycemic symptoms occur often varies quite markedly.<sup>12-15</sup>

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occur when the blood sugar level reached its lowest point and remained elevated until the normal blood sugar level was reached. The rise in the systolic pressure was approximately six times as great as the diastolic. It is interesting that this phenomenon was accentuated in patients with essential hypertension and absent in those with Addison's disease.

The action of the sympathetic nervous system as well as the thyroid secretion in the maintenance of the blood sugar level is apparently similar to that of the adrenal medulla. Further evidence that this is true will be considered later in this paper.

Macleod<sup>51</sup> has recently advanced the hypothesis of a center for the regulation of carbohydrate metabolism which he localizes in the pons. More recently, Ingram and Barris<sup>52</sup> have shown that in rats in which severe lesions were produced in the hypothalamus there was a definite tendency toward hypoglycemia with sensitivity to insulin.

It is quite obvious from the above discussion of the various factors at play in the maintenance of the normal blood sugar level that this is not a simple process but a complex one. That the islets of Langerhans play only one part in this mechanism is quite evident. The conception, therefore, of the hypoglycemic state as being the result of an excessive secretion of insulin is entirely too rigid an approach to the subject. There are many cases in which this is apparently true. Oftentimes some other explanation must be sought.<sup>53</sup>

#### SYMPTOMS

The earlier cases of hypoglycemia that were reported were quite clear-cut in their symptomatology. As other observations have been added, the symptomatology has become protean in its scope.<sup>70</sup> As a general rule—and there are many exceptions—symptoms are seen more frequently when the glycogen reserve in the liver is low, as is often the case in fasting, violent exercise, exposure to cold, and undue excitement.

An accurate classification of these symptoms is difficult. Many of them come about as a result of the effort on the part of the body to elevate the level of sugar in the blood. Others are the result of the hypoglycemia per se. Many articles have called attention to the similarity of the early findings to those of increased adrenalinemia, such as sweating, pallor, tremor, tachycardia, elevation of blood pressure, and fear. Recent contributions have offered further clinical substantiation of this. Wegierko<sup>74</sup> has recently observed three patients suffering from bronchial asthma, all of whom have been relieved for a considerable length of time following the production of hypoglycemic shock with insulin. Duneau<sup>75</sup> had under his care a patient who became angered because he was considered drunk during a hypoglycemic phase with immediate recovery from the hypoglycemia. While bradycardia has been observed,<sup>76</sup> this is not the general rule. Not only is tachycardia more common, but we have seen rather characteristic anginoid attacks

excretion; and ketonuria does not appear or is very much reduced. These changes are the result of removal of the anterior lobe of the hypophysis, as the retention of the posterior lobe apparently has no effect on the course of the diabetes. Such findings are in accord with the observations that a crude alkaline or acid extract of the anterior lobe of the hypophysis will produce hyperglycemia and glycosuria in normal dogs,<sup>38-44</sup> although no effects have been noted in rats when various types of commercial extracts have been used.<sup>45</sup> Considerable effort has been directed toward obtaining a relatively pure "diabetogenic" principle from anterior hypophyseal extracts with only a moderate amount of success. In his discussion of the nature of this substance,<sup>46</sup> Long is of the opinion that "one component of the 'diabetogenic' action of the anterior pituitary is prolactin or some substance that becomes closely associated with it in the methods at present used in its preparation."

The action of the cortex of the adrenal gland on carbohydrate metabolism resembles to a large extent that of the anterior lobe of the hypophysis. A review of the earlier experiments on this phase of metabolism has been recently published by Long and Lukens<sup>47</sup> and need not be repeated here. It is largely due to these two investigators and their colleagues that much light has been thrown on this problem. In his recent Harvey Lecture, Long<sup>48</sup> describes in detail this action. The effect of removal of the adrenal medulla apparently plays no important part in the amelioration of the symptoms of pancreatic diabetes. This function rests solely in the adrenal cortex. The effect on the depancreatized animal is so nearly identical with that of the anterior hypophysis that he raises the question as to a similar process being involved. In view of the fact that active extracts of the hypophysis of the "diabetogenic" type, capable of producing glycosuria in hypophysectomized-depancreatized cats, lose their action in the absence of the adrenal cortex, it is highly suggestive that this hypophyseal influence on carbohydrate metabolism takes place through intermediary action on the cortex of the adrenal gland.

There are other and divergent views as to the mode of action of both the hypophysis and the adrenal cortex. These need not be discussed at this time.

The action of the adrenal medulla in hypoglycemia is apparently a secondary one, having as its function the mobilization of sugar from the liver. Since Cannon developed this conception several years ago in relation to experimental hypoglycemia in dogs,<sup>49</sup> it has been elaborated upon, but has not been changed in its fundamental features. This increased output of adrenalin in hypoglycemia is not only associated with a rise in ventricular rate, but likewise in cardiac minute volume output. The hypoglycemia per se, however, apparently has a deleterious effect on the myocardium.<sup>50</sup> When hypoglycemia was induced in normal individuals with insulin given intravenously,<sup>50</sup> a rise in blood pressure was seen to

occur when the blood sugar level reached its lowest point and remained elevated until the normal blood sugar level was reached. The rise in the systolic pressure was approximately six times as great as the diastolic. It is interesting that this phenomenon was accentuated in patients with essential hypertension and absent in those with Addison's disease.

The action of the sympathetic nervous system as well as the thyroid secretion in the maintenance of the blood sugar level is apparently similar to that of the adrenal medulla. Further evidence that this is true will be considered later in this paper.

Macleod<sup>51</sup> has recently advanced the hypothesis of a center for the regulation of carbohydrate metabolism which he localizes in the pons. More recently, Ingram and Barris<sup>52</sup> have shown that in rats in which severe lesions were produced in the hypothalamus there was a definite tendency toward hypoglycemia with sensitivity to insulin.

It is quite obvious from the above discussion of the various factors at play in the maintenance of the normal blood sugar level that this is not a simple process but a complex one. That the islets of Langerhans play only one part in this mechanism is quite evident. The conception, therefore, of the hypoglycemic state as being the result of an excessive secretion of insulin is entirely too rigid an approach to the subject. There are many cases in which this is apparently true. Oftentimes some other explanation must be sought.<sup>53</sup>

#### SYMPTOMS

The earlier cases of hypoglycemia that were reported were quite clear-cut in their symptomatology. As other observations have been added, the symptomatology has become protean in its scope.<sup>54</sup> As a general rule—and there are many exceptions—symptoms are seen more frequently when the glycogen reserve in the liver is low, as is often the case in fasting, violent exercise, exposure to cold, and undue excitement.

An accurate classification of these symptoms is difficult. Many of them come about as a result of the effort on the part of the body to elevate the level of sugar in the blood. Others are the result of the hypoglycemia per se. Many articles have called attention to the marked similarity of the early findings to those of increased adrenalinemia, such as sweating, pallor, tremor, tachycardia, elevation of blood pressure, and fear. Recent contributions have offered further clinical substantiation of this. Wegierko<sup>55</sup> has recently observed three patients suffering from bronchial asthma, all of whom have been relieved for a considerable length of time following the production of hypoglycemic shock with insulin. Duncan<sup>56</sup> had under his care a patient who became angered because he was considered drunk during a hypoglycemic phase with immediate recovery from the hypoglycemia. While bradycardia has been observed,<sup>56</sup> this is not the general rule. Not only is tachycardia more common, but we have seen rather characteristic anginoid attacks

during the hypoglycemic phase similar to those seen in coronary insufficiency during emotional stress. This has been observed by others.<sup>57</sup> The gastrointestinal manifestations are not so easily explained. These vary from mild dyspepsia to intense abdominal pain, often resulting in needless abdominal operations. In view of the fact that increased intestinal motility has been observed in the hypoglycemic state, it is quite possible that the explanation may rest here. One of my earlier cases had had a previous cholecystectomy before he came to me and another an appendectomy. Bickel<sup>58</sup> observed two patients, one of whom presented the features characteristic of peptic ulcer and the other those of biliary colic. Both presented hypoglycemia and were relieved of their symptoms with adequate dietary measures for this condition. This aspect of the symptomatology has recently been reviewed quite adequately by Harris.<sup>59</sup>

The neuropsychiatric manifestations of this disease are most confusing. These may vary from diplopia and dizziness to personality changes, convulsions, and coma. Harris has recently reviewed these neurologic aspects<sup>60, 61</sup> and states that hyperinsulinism may simulate any of the neuroses or psychoses. At the same time it must constantly be borne in mind that many of these psychoses likewise show alterations in sugar tolerance. While emotional disturbances of a severe nature in those people free from mental disease is frequently accompanied by hyperglycemia, similar emotional disturbances in the mentally disordered usually do not show this change.<sup>62</sup> A variety of mental disorders have been studied during the past few years and the reports for the most part are contradictory.<sup>63-72</sup> While mental deterioration has been observed in patients with severe hypoglycemia,<sup>165, 166</sup> it does not follow that all patients with severe mental deterioration and hypoglycemia present a causal relationship. At the present time this offers one of the most difficult problems in differential diagnosis. If the mental disorder is secondary to the hypoglycemia, marked improvement often follows adequate medical or surgical treatment. If the hypoglycemia is an associated part of the psychosis, such treatment is generally of little permanent benefit.

Especially in the interpretation of epileptic convulsions have difficulties been encountered. Shortly after it became apparent that overdosage of insulin was associated with epileptiform seizures, patients with idiopathic epilepsy began to be studied with an idea of derangement of carbohydrate metabolism. One of the earliest papers on the subject was that of Daley, Pryde, and Walker,<sup>107</sup> who found equivocal sugar values. Lennox, in his studies on blood sugar in this type of patient,<sup>168, 169</sup> is of the opinion that the great majority of them show no fundamental disturbance and that changes when they do occur are for the most part the result of convulsive seizures rather than the cause. Nielsen,<sup>170</sup> however, found 90 per cent of his cases of idiopathic epilepsy

showing a tendency to hypoglycemia, although he does not consider that this alone is sufficient to produce an attack. He is of the opinion that the determination of the fasting sugar level, or even the sugar tolerance in such a patient, gives insufficient grounds for making a diagnosis of hyperinsulinism. My experience is in accord with this attitude. At the same time, it must not be forgotten that true hyperinsulinism mimics idiopathic epilepsy remarkably, and we have reported previously on cases so diagnosed. The experience of Whipple and his coworkers<sup>5</sup> along this line is dramatic.

The mechanism of the production of convulsive seizures in hypoglycemia is as yet not fully understood. Wohlwill<sup>171</sup> noticed changes in ganglion cells as well as ameboid changes in glial cells. Terplan<sup>172</sup> has verified these findings, noting especially changes in the occipital and frontal lobes and in the island of Reil and in the hippocampal gyrus. There was likewise considerable cerebral edema, a finding that might be used to explain occasional hypoglycemic headaches.<sup>173</sup> While post-mortem change must always be taken into consideration in the explanation of such pathologic findings,<sup>73</sup> experimental results tend to corroborate them. Grayzel<sup>74</sup> found that in rabbits those animals with hypoglycemia without convulsions showed no lesions, while those with convulsions presented hyperchromatic cells with cork-screw processes, and in those in which convulsions were most severe actual necrobiosis took place. The cells chiefly involved were particularly the pyramidal cells of the third and fifth cortical layers. He suggests that these changes may be the result of anoxemia and ischemia following circulatory changes produced by the convulsive seizures.

Olmsted and Logan demonstrated several years ago<sup>75</sup> that insulin convulsions probably had their origin in the respiratory center and were the result of anoxemia, while Holmes<sup>76</sup> showed that the consumption of oxygen in the gray matter was greater in the presence of glucose and was dependent upon the formation of lactic acid from glucose. These findings have been generally corroborated by Woris.<sup>77</sup> The subject of the mechanism of the production of neurologic symptoms in hypoglycemia has been recently adequately discussed by Dameshek and Myerson.<sup>78</sup>

#### CLINICAL TYPES

A detailed discussion of the various clinical types that have been only recently described cannot be undertaken here. The reader is referred to numerous excellent reports<sup>79-88</sup> for a full description of various cases as well as interpretations of the hypoglycemic state.

Generally, hypoglycemia can be divided into two types, those cases associated with no demonstrable pancreatic lesion and those in which morphologic changes are demonstrable in the pancreas.



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interesting. Ordinarily, it apparently aids in mobilizing sugar from the liver as do the adrenal medulla and the sympathetic nervous system. Because of this, when the thyroid is removed in a normal animal, there is generally an increase in sugar tolerance and a definite sensitivity toward the action of insulin. In hyperactive thyroid states, such as Graves' disease, the opposite is true. Occasionally in hypoglycemia, this glycogenolytic function of the thyroid may be necessary in the maintenance of normal blood sugar levels, and at such times the hypoglycemic patient may present an increased basal metabolism and other signs of thyroid hyperactivity. Recently with W. H. Cole I have reported on clinical observations of this type with a brief review of the action of the thyroid gland in this respect.<sup>124</sup> The case reported by Aitken<sup>125</sup> seems to fall in this group. The patient described by Gilmour and Walton<sup>126</sup> is interesting in this respect, in view of the fact that along with the nervous symptoms that were present the basal metabolism was increased 20 per cent. After removal of an adenoma of the islet cell type with relief of the hypoglycemia, the basal metabolism fell to minus 26 per cent, subsequently rising to minus 9 per cent.

Menstrual hypoglycemia and lowered blood sugar values associated with various types of vegetative imbalance have been recently described.<sup>127, 128</sup>

Besides these above hypoglycemic states obviously extrapancreatic in origin, there occurs a large group of patients presenting varying degrees of hypoglycemia in which no abnormality can be found either in the pancreas or in any of the other endocrine glands or the liver. The origin of this carbohydrate imbalance is difficult to explain at the present time, just as is the origin of a large group of cases of diabetes mellitus. Until more sensitive methods of differential study are developed, the interpretation of the origin of the lowered blood sugar will be difficult. This is of great clinical importance in view of the fact that often some of these patients resemble closely those with pancreatic islet hyperplasias.

Three types of anatomic change have been described in the islets of Langerhans in patients with severe hypoglycemia. The first of these is one of generalized hypertrophy and hyperplasia of the islet tissue. In most of the patients so described, the lesion has been found shortly after birth or in infancy and has often been present in the offspring of diabetic mothers. This is interesting in consideration of the fact that Bensley demonstrated a number of years ago that in cases of dire necessity additional islet tissue could be formed from regenerating ducts. Further evidence that this hyperplasia is a compensatory phenomenon can be seen in the rapidity with which such hypoglycemic infants develop a stabilized carbohydrate metabolism following the institution of suitable dietary measures.

Another type of organic change seen in the pancreas in hypoglycemia is that of the so-called adenoma which is generally composed of beta

In the first group, juvenile hypoglycemia has received considerable attention during the past few years. Because of the frequency of convulsions in childhood, efforts were made relatively early to establish some relationship with altered carbohydrate metabolism. Often this could not be done. At the same time, autopsy reports of diffuse hyperplasia of the islet tissue began to appear in the literature just as did examples of congenital aplasia of the islets of Langerhans.<sup>99</sup> Others have appeared since those described in earlier reviews of the subject.<sup>100, 101</sup> Just as these cases began to be recognized earlier, so many of them have been treated successfully with adequate dietary measures. Especially has this been true of those infants born of diabetic mothers, a situation that is becoming more frequent since the advent of insulin. The effect of the ketogenic diet on the blood sugar of children has been recently studied by Talbot and Bates<sup>104</sup> and the entire subject of infantile hypoglycemia reviewed by others.<sup>105-107</sup> Darrow<sup>108</sup> has observed two children with convulsions associated with hypoglycemia and mental deficiency with x-ray evidence of anatomic lesions in the brain. It is suggested that the disturbance in the regulation of the blood sugar may have its origin in the cerebral lesions. This recalls the dramatic case reported by Graham and Hartmann<sup>109</sup> in which an infant with mental deterioration and a profound state of hypoglycemia that did not respond to dietary measures was greatly improved following subtotal resection of the pancreas. Congenital defects in the glycogen mechanism of the liver are likewise responsible for hypoglycemic states in infants. The first of these, described by von Gierke<sup>110</sup> as hepatonephromegalia glycogenica, is probably the result of the inability of the liver to discharge glycogen. An opposite condition, the failure of the liver to convert glucose to glycogen, with a resultant fatty infiltration of the liver has likewise been recently described.<sup>111</sup>

In the adult, hypoglycemia resulting from various hepatic disorders is well known. Primary carcinoma of the liver,<sup>112-114</sup> various types of atrophy of the liver,<sup>115-117</sup> fatty infiltration,<sup>118</sup> and toxic hepatitis following the administration of neoarsphenamine have been recently reported. Interestingly enough, however, thrombosis of the hepatic artery in a diabetic patient has been followed by a sudden marked resistance to insulin.<sup>120</sup> This could possibly be explained on the basis of the associated gangrene of the pylorus that was present and the associated toxemia. The presence of hypoglycemia in such hepatic disorders is generally a concomitant finding, found with other evidence of severe liver insufficiency, and, as a rule, causes no interpretative difficulties.

Thyroid, hypophyseal, and adrenal cortical insufficiencies are often associated either with hypoglycemic symptoms or hypoglycemic sugar tolerance curves.<sup>117, 121-123</sup> Generally, related clinical findings are present. Because of the interrelationships of these endocrine glands, pure types are often not seen. The action of the thyroid gland is at times

adenomas has been cultured *in vitro* successfully. Subsequent transplants of this cultured tissue into diabetic patients failed to produce clinical improvement in the diabetes.<sup>151</sup>

Because of the cytologic similarity of many of the benign growths to carcinoma, the diagnosis of malignant disease must be made with care. Before making such a diagnosis, we prefer to have present (1) invasion of the capsule associated with (2) invasion of blood vessels or with (3) metastases.

#### DIAGNOSIS

Since the symptoms produced by hypoglycemia are caused by a lowered level of sugar in the blood, it is of the utmost importance that the presence of such symptoms be related directly to the hypoglycemia. The production of hypoglycemia, either with insulin or by fasting, offers an excellent opportunity to reproduce the symptom-complex.

Single fasting sugar determinations are of little value. Even glucose tolerance curves are often confusing in their interpretation. In a recent study of the respiratory metabolism in hyperinsulinism following the ingestion of glucose, Rabinowitch and Fowler<sup>152</sup> concluded that flat sugar curves were evidence of hyperinsulinism. They draw attention to the fact that the type of curve obtained depends upon whether the converted glycogen is to be used for storage or oxidation, and this in turn is determined by the amount of glycogen present in the liver before the glucose is ingested.

Insulin tolerance tests have generally been within normal limits in those patients in whom tumors have been subsequently found. Abnormal sensitivity or resistance to insulin is highly suggestive of extrapancreatic origin of the hypoglycemia. This is likewise true of the action of adrenalin. Failure of adrenalin to elevate the level of sugar in the blood has generally been ascribed to lowered glycogen reserve in the liver. That this may not always be the case is suggested by the work of Cope and Marks,<sup>153</sup> who found that in the absence of the anterior lobe of the hypophysis the liver glycogen is not discharged in the usual manner. In an unpublished observation in a patient with hypoglycemia showing clinical evidence of anterior hypophyseal insufficiency, however, I found no difference in the amount and rate in the glycogen discharge after the injection of adrenalin. It is highly probable that, although there was hypophyseal insufficiency present, this was not of a degree severe enough to produce the abnormality as described above. A better explanation, however, is offered in the recent results of Russell and Cori,<sup>154</sup> who have demonstrated that the difference in the glycogenolytic effect of adrenalin in the normal and hypophysectomized animals is due to a diminished rate of absorption of the adrenalin from the subcutaneous tissue in the hypophysectomized animal. In several instances I have observed a split action on the part of the adrenalin in the sense that the pressor effect,

cells or of cells tending to resemble this type. Whipple and Frantz<sup>4</sup> were able to collect 21 cases in which this type of tumor was found at operation and 10 cases found at autopsy, all producing hypoglycemic symptoms. To this series I have been able to add 14 additional cases reported in the literature since then.<sup>125, 126, 129-139</sup> Obviously, this by no means represents all of the instances that have been observed. The lesion is being encountered often enough to prevent the reporting of numerous single cases that have been seen.

Cancer of the islet cell type presents the most profound states of hypoglycemia that are encountered clinically. Evangelisti,<sup>140</sup> in a fairly complete review of the literature, was able to collect only 8 cases to which he added a single case. To add to this series, I have been able to collect 4 additional cases.<sup>141-144</sup> This type of carcinoma is apparently extremely rare, and for this reason it is interesting to note its occurrence as well as that of the benign adenoma spontaneously in animals.<sup>145-147</sup>

#### PATHOLOGY

The proper study of the cellular changes in the islets of Langerhans as a rule requires more elaborate technical methods than are used in the ordinary study of pathologic tissue. Earlier studies on this aspect of the pancreas have been described by Bensley<sup>148</sup> and a later, more brief but adequate review may be found in Cowdry's recent *Textbook of Histology*,<sup>149</sup> and in the article by Bagley.<sup>174</sup> There is definite need at the present time for more data on the individual cell types in the islets, especially in those patients in whom there is clinical evidence of hypoglycemia, but in whom no tumors have been found. In one of my unpublished cases, there was an increase in the relative proportion of the alpha cells and in another there was a tendency to vacuolization of the beta cells, suggesting overwork.

The cytologic picture in adenomas of the islets has been described in detail by O'Leary and myself<sup>150</sup> and by Whipple and Frantz.<sup>5</sup> The tumors may be single or multiple. They vary in size from a few millimeters to many centimeters, but as a rule they tend to be unusually small. While generally encapsulated, this is not always true. When seen grossly in the pancreas, the appearance is that of a localized, elevated, cyanotic area, at times resembling a hematoma. Microscopically, in our experience, the majority cell type, if not identical, was closely related to the beta cell in staining characteristics. Generally speaking, the toxicity of the tumor depends more upon the maturity of this differentiation toward the beta cell than it does upon the size of the tumor. Degenerative and hemorrhagic areas are frequently encountered, as is hyalinization. We have seen this latter phenomenon apparently completely replace such an adenoma. Interesting enough, the islet tissue removed from the normal pancreas, away from a functioning adenoma, is apparently normal in every respect. Tissue from two islet cell

If no apparent tumor is present, the question of partial resection of the pancreas must be considered. The reports of the efficacy of such a procedure are equivocal.<sup>158-162</sup> As Rosecoe Graham has pointed out,<sup>158</sup> it is quite possible for a pancreas with normal appearing islets anatomically to show on assay an insulin content that is much greater than normal. As a general rule, those instances in which less than one-half of the pancreas has been removed have been associated with unsatisfactory results. There are many reports, however, in which a satisfactory result has followed the extirpation of a larger amount of the pancreas. Whether the results here can be considered in terms of proportion of the pancreas removed cannot be definitely determined until the accumulation of more complete data. The attitude at present cannot be dogmatic; however, the analogy of removal of pancreatic tissue in hypoglycemia to the giving of insulin in diabetes mellitus suggests that it is a question of dosage. Just as an insufficient amount of insulin in the treatment of diabetes mellitus is of little value, so removal of an insufficient amount of pancreatic tissue in hypoglycemia would be of little value. Comparison has been made in times past with the thyroid gland in Graves' disease. The accomplishment of adequate therapeutic results in the surgical treatment of hyperfunctioning of the thyroid gland is most often associated with subtotal thyroidectomy. It was this conception that led Graham and Hartman<sup>160</sup> to deliberately operate upon an infant in order to remove an enormous amount of pancreas tissue.

The operation of partial pancreatectomy is often quite difficult technically, especially in adipose, hypersthenic types. The danger of injury to the splenic vein is a definite one. Where this has been done and ligation is necessary, if the spleen cannot be easily removed as has been suggested by Holman, collateral circulation may be established by scarifying the spleen and covering it with omentum.

The presence of pancreatic cysts and fistulas does not, as a rule, present a serious problem.<sup>163</sup>

Any surgical procedure in which the liver is deficient in glycogen may be dangerous. Because of the frequency with which the glycogen reserve may be used up in the hypoglycemic patient, much care must be used in this regard. While this has been a clinical observation for some time, the experimental work of Kosterlitz<sup>164</sup> is especially interesting. He noted that in the fed rat, where there is ample liver glycogen, a fall in blood pressure below a critical point is accompanied by hyperglycemia. In the fasted rat, however, with the liver glycogen reduced to a minimum, a fall in blood pressure below such a critical value is associated with a rapid decrease in the blood sugar level, probably due to the suppression of gluconeogenesis consequent to the fall in blood pressure. Upon restoring the blood pressure to its normal level with aëmia or blood transfusion, the normal sugar level is established.



as evidenced by blood pressure readings and the pulse rate, did not necessarily parallel the glycogenolytic effect of the adrenalin. In none of these cases was there sufficient evidence of tumor to warrant exploration.

The differentiation between the presence or absence of tumor cannot be made with any degree of certainty, at the present time, before operation. In no case in which there was considerable doubt as to the presence of tumor before operation have I encountered one at exploration.

#### TREATMENT

In consideration of the treatment of hypoglycemia, the conception of this condition as the antithesis of diabetes mellitus can again be used. Originally, medical therapy was directed at a high carbohydrate diet. It was soon found, however, that while this was excellent therapy for the acute shock, it eventually led to an increase in the carbohydrate tolerance with resulting increase in the frequency and severity of the attacks. A diet relatively low in carbohydrates and high in fats was substituted with much better effect. The action of such a diet on glucose tolerance has been described by Clark and Greene.<sup>154</sup> John<sup>155</sup> added to such a regimen twenty units of insulin one-half hour after each meal with excellent results. It is his opinion that such treatment has but little effect on the anatomic type of hypoglycemia and thus can be used as a means of differentiation from the functional type. Conn<sup>156</sup> has recently suggested the use of a high protein diet in the treatment of spontaneous hypoglycemia, based on the facts that it causes no hyperglycemia and thus avoids excessive production of insulin and secondary hypoglycemia; it provides a source of glucose over a long period of time and thus allows severe cases further restriction of carbohydrates than could otherwise be effected.

With the rationalization of dietary treatment of the condition, the necessity of surgical intervention has become much less, just as has the use of similar dietary methods in the treatment of diabetes mellitus reduced the number of patients in which the use of insulin is an absolute necessity. There are times, however, when the use of large amounts of insulin is necessary in diabetes, and likewise in hypoglycemia there are times when the most carefully carried out dietary regimen is not sufficient. While x-ray therapy has been suggested,<sup>157</sup> most opinions favor surgical exploration in such cases.

The surgical technique employed in such explorations is not extraordinary and has been sufficiently described in many of the above references. If a localized tumor is found, it is generally located either in the tail or the body, though not necessarily so. The head of the pancreas should always be explored, regardless of whether a lesion is encountered elsewhere or not. There are several reports on record of multiple tumors.

If no apparent tumor is present, the question of partial resection of the pancreas must be considered. The reports of the efficacy of such a procedure are equivocal.<sup>158-162</sup> As Rosecoe Graham has pointed out,<sup>158</sup> it is quite possible for a pancreas with normal appearing islets anatomically to show on assay an insulin content that is much greater than normal. As a general rule, those instances in which less than one-half of the pancreas has been removed have been associated with unsatisfactory results. There are many reports, however, in which a satisfactory result has followed the extirpation of a larger amount of the pancreas. Whether the results here can be considered in terms of proportion of the pancreas removed cannot be definitely determined until the accumulation of more complete data. The attitude at present cannot be dogmatic; however, the analogy of removal of pancreatic tissue in hypoglycemia to the giving of insulin in diabetes mellitus suggests that it is a question of dosage. Just as an insufficient amount of insulin in the treatment of diabetes mellitus is of little value, so removal of an insufficient amount of pancreatic tissue in hypoglycemia would be of little value. Comparison has been made in times past with the thyroid gland in Graves' disease. The accomplishment of adequate therapeutic results in the surgical treatment of hyperfunctioning of the thyroid gland is most often associated with subtotal thyroidectomy. It was this conception that led Graham and Hartman<sup>100</sup> to deliberately operate upon an infant in order to remove an enormous amount of pancreas tissue.

The operation of partial pancreatectomy is often quite difficult technically, especially in adipose, hypersthenic types. The danger of injury to the splenic vein is a definite one. Where this has been done and ligation is necessary, if the spleen cannot be easily removed as has been suggested by Holman, collateral circulation may be established by scarifying the spleen and covering it with omentum.

The presence of pancreatic cysts and fistulas does not, as a rule, present a serious problem.<sup>163</sup>

Any surgical procedure in which the liver is deficient in glycogen may be dangerous. Because of the frequency with which the glycogen reserve may be used up in the hypoglycemic patient, much care must be used in this regard. While this has been a clinical observation for some time, the experimental work of Kosterlitz<sup>164</sup> is especially interesting. He noted that in the fed rat, where there is ample liver glycogen, a fall in blood pressure below a critical point is accompanied by hyperglycemia. In the fasted rat, however, with the liver glycogen reduced to a minimum, a fall in blood pressure below such a critical value is associated with a rapid decrease in the blood sugar level, probably due to the suppression of gluconeogenesis consequent to the fall in blood pressure. Upon restoring the blood pressure to its normal level with acacia or blood transfusion, the normal sugar level is established.

as evidenced by blood pressure readings and the pulse rate, did not necessarily parallel the glycogenolytic effect of the adrenalin. In none of these cases was there sufficient evidence of tumor to warrant exploration.

The differentiation between the presence or absence of tumor cannot be made with any degree of certainty, at the present time, before operation. In no case in which there was considerable doubt as to the presence of tumor before operation have I encountered one at exploration.

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cure of prolapse. Many other operations were utilized as in the previous series. A comparison of the results obtained is presented.

**The Continuous Auscultation of the Fetal Heart by Means of an Amplifying Stethoscope (Preliminary Report).** By Dr. Harvey B. Matthews, Brooklyn, N. Y.: The importance of the continuous auscultation of the fetal heart is unquestionable. Early manifestations of fetal distress could be more often recognized if it were possible to continuously auscultate the fetal heart. An amplifying stethoscope conducting the output through a loud speaker has been devised by means of which this can be accomplished. After placing the receiving diaphragm over the fetal heart i.e., the area of the mother's abdomen where the fetal heart is loudest, the operation is simple: plug in, tune in, and listen.

**Symposium on Eclampsia: The Prevention of Eclampsia.** By Prof. K. de Snoo, Utrecht, Holland: The author presents his experience in over twenty-five years in 2,000 women with toxemia. His theories concerning eclampsia are discussed and his routine treatment presented. Prenatal care inside and outside the clinics is pictured. In Holland the prenatal care outside the clinics is chiefly in the hands of midwives who have learned to measure blood pressure and to examine urine. There is a league for prenatal care which organizes and supervises the regular examinations. The public in Holland has gradually been educated to expect prenatal care. In 175,000 births, the mortality from eclampsia is approximately 1 in 3,000.

**Analgesia and Anesthesia and Their Bearing Upon the Problem of Shortened Labor.** By Dr. Arthur H. Bill, Cleveland, Ohio: The conduct of painless labor is not an experiment and has not been such for the last twenty or twenty-five years. Labor may be made practically painless and delivery performed under anesthesia safely for mother and child. Some unfavorable results of childbirth have been unjustly attributed to analgesia and anesthesia. The question today is not whether we can make labor painless, but what the proper choice of methods for accomplishing this should be. No single method will serve every case well and no single method is suitable for the conduct of the entire labor. A proper combination of methods is to be preferred. The combination depends upon the character of the labor, whether first stage or second stage, and whether the patient is a primipara or a multipara. Drugs promoting analgesia or anesthesia are essentially suitable only for the first stage. The general anesthetics are to be preferred for the second stage and delivery; however, the latter may be used during a varying part of the first stage. From a strictly obstetric point of view, the general anesthetics are of two types, depending upon whether they do or do not cause complete relaxation of the uterus. The advantages of each are illustrated. A proper choice in the individual case is important. Painless labor does not lead to meddlesome interference. Often quite the opposite is true. The best way to insure a spontaneous course of the first stage is to make it painless. Interference is usually promoted by a desire to relieve suffering. The birth may be spontaneous or not, depending upon the judgment of the obstetrician more than upon the anesthesia.

**A Study of the Hormonal Content of Ovarian Cysts.** By Dr. Fred L. Adair, Chicago, Ill.: About 200 specimens of fluid obtained from cystic genital tumors have been studied chiefly for the presence of estrogenic substance. Most of these tumors are usually classed as of ovarian origin. These findings have been compared with the gross and microscopic appearance of the fluids and tissues obtained at operation. Some fluids show it in high degrees of concentration and others show this substance in very low concentration or not at all. This suggests that certain fluids contain an amount of this substance comparable to that present in other

# Review of Recent Meetings

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## SIXTY-SECOND ANNUAL MEETING OF THE AMERICAN GYNECOLOGICAL SOCIETY

SWAMPSCOTT, MASS., MAY 31, JUNE 1 AND 2, 1937

WILLIAM J. DIECKMANN, M.D., CHICAGO, ILL.

*(From the Department of Obstetrics and Gynecology, the University of Chicago)*

**The Upper Pelvic Floor, and Its Importance in Total Abdominal Hysterectomy.** By Dr. Lillian K. P. Farrar, New York, N. Y.: The term upper pelvic floor is intended to include all the tissues attached to the cervical portion of the uterus including the nerves, lymphatics, blood vessels, and ureters lying in the broad ligaments, the adjacent muscles which are adherent to the broad ligaments by their fascial coverings and the muscles which are attached to the vagina and thereby contribute to the support of the uterus. If a technique is followed in total abdominal hysterectomy that is very similar to that commonly employed in vaginal hysterectomy, the uterus may be removed with little injury to the upper pelvic floor and with good conservation of the supporting structures which remain.

**A Modification of the Le Fort Operation Which Greatly Increases Its Scope.** By Dr. J. R. Goodall, Montreal, Quebec: The Le Fort operation consists of a marsupialization of the vagina to correct procidentia. It has its well-defined limitations. It is restricted more or less to women past the menopause, and preferably to elderly widows. In the present modification, it is imperative only that the patient be sterile. The marsupialization is restricted to the vault of the vagina, descending a distance that will vary with the vaginal capacity. The further narrowing of the vagina below this is continued by an anterior colporrhaphy and perineorrhaphy. The upper marsupialization forms an excellent point d'appui and does not interfere with marital relations. The modification finds its best application following vaginal hysterectomy in complete procidentia.

**An Efficient Composite Operation for Uterine Prolapse.** By Dr. Edward H. Richardson, Baltimore, Md.: Complexity of the surgical problem presented by advanced grade vaginal hernias was stressed. No single plan of reconstruction surgery has been devised yet that is applicable to all types. Indications vary in the two age groups. There was discussion of several factors involved and enumeration of the various operations commonly employed today with a brief discussion of the rational use and limitations of each. The need for a composite operation, its scope and aim were considered and the technique described.

**Prolapse of the Uterus—Shifting Trends in Treatment.** By Dr. Joseph L. Baer, Chicago, Ill.: During the years 1929 to 1935, inclusive, 221 operations for the cure of prolapse were performed by the gynecologic staff of Michael Reese Hospital. A comparable series of 220 operations was reported before this Society in 1925. In the original series interposition was the operation of choice; whereas, vaginal hysterectomy exhibited in the literature current ten years ago led to the spontaneous introduction of vaginal hysterectomy as the method of choice at Michael Reese Hospital for the

cure of prolapse. Many other operations were utilized as in the previous series. A comparison of the results obtained is presented.

**The Continuous Auscultation of the Fetal Heart by Means of an Amplifying Stethoscope (Preliminary Report).** By Dr. Harvey B. Matthews, Brooklyn, N. Y.: The importance of the continuous auscultation of the fetal heart is unquestionable. Early manifestations of fetal distress could be more often recognized if it were possible to continuously auscultate the fetal heart. An amplifying stethoscope conducting the output through a loud speaker has been devised by means of which this can be accomplished. After placing the receiving diaphragm over the fetal heart i.e., the area of the mother's abdomen where the fetal heart is loudest, the operation is simple: plug in, tune in, and listen.

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tissues and that it is probably extrinsic in origin. Other cysts appear to secrete this estrogenic substance and it is therefore intrinsic in origin.

**Observations Pertinent to Gonadotropic Therapy in Gynecology.** By Dr. Robert A. Ross, Durham, N. C.: For the past six years Dr. Ross and his coworkers have studied ovaries and endometria of patients who had received injections of gonadotropic principles. They were concerned originally with the possibility that some of the effects observed in animals might occur in the human. Later they have tried to explain such paradoxes as instances of clinical improvement without significant histologic changes. Recent studies have concerned primarily responses in anovulatory states. An attempt to employ the endometrium as an indicator of the levels of ovarian function has resulted in an alteration of their classification of endometrial patterns. These studies have suggested, in addition, an avenue which may help ascertain the required clinical dose of these preparations. Such a dose is influenced by various factors which include the age of the patient, associated pelvic conditions, as well as individual tissue receptivity.

**The Clinical Significance of Endometrial Hyperplasia.** By Dr. Franklin L. Payne, Philadelphia, Pa.: The statement that endometrial hyperplasia does not necessitate abnormal uterine bleeding is proved in this study. The material consists of 496 premenopausal and 38 postmenopausal specimens of endometrial hyperplasia. Analysis of the premenopausal hyperplasia group shows that abnormal uterine bleeding occurred in 85.2 per cent of the patients, the remainder having normal, scanty, or absent periods. The incidence of hyperplasia in the clinical conditions which are commonly associated with it and the incidence of abnormal bleeding in these conditions are shown. The association of fundal malignancy with both pre- and postmenopausal hyperplasia is discussed. Analysis of the postmenopausal group shows hyperplasia to occur either with or without demonstrable pelvic pathology and often in the absence of uterine bleeding.

**An Unusual Obstetrical Injury, Detaching Bladder and Urethra From the Symphysis Pubis and Causing Complete Epispadias.** By Dr. Guy L. Hunner, Baltimore, Md.: A primipara, aged thirty-eight years, with adequate pelvic measurements, in a spontaneous delivery of an 8.5 pound boy, with R. O. A. position, remained in the second stage of labor sixty-six hours. After complete dilatation of the cervix and spontaneous rupture of the membranes, there was precipitate birth. Dr. Hunner described the injury, particularly to the urethra, as well as the subsequent treatment and results.

**Presidential Address.** By Dr. Fred J. Taussig, St. Louis, Mo.: An excellent résumé of the history of eclampsia, toxemia of pregnancy, and prenatal care.

**Pregnancy Complicated by Ovarian Tumors.** By Dr. Karl M. Wilson, Rochester, N. Y.: Such tumors complicating pregnancy may at times cause no trouble, but more often they are to be regarded as a serious menace. Formerly, the mortality associated with this complication was high, but modern surgical methods have reduced this considerably. The principal dangers lie in abortion, torsion of the pedicle of the tumor, or the production of a mechanical obstacle to labor. A series of twenty-eight cases from the author's service is presented. In this small series all the above complications were noted. The most interesting group in the series is found in those patients where removal of the tumor necessitated removal of the corpus luteum. There is a discussion of the indications and time for operation. There were no deaths in the series.

**Biologic and Clinical Import of Vulvovaginal Mycosis.** By Dr. H. Close Hessel-tine, Chicago, Ill.: A brief review was given. The variable incidences, methods of spread, and influence of physiologic states of the vulva and vagina were explained. Methods for identification of the medical monilia and cryptococci were discussed. The significance of the disease and a similarity of certain vulva mycoses to early stages of kraurosis were emphasized. Tables illustrated the fungicidal potency of element iodine and data showed the therapeutic value of potassium iodide-potassium iodate mixture in a neutral inert diluent. Some metabolic products from glucose by these fungi were suggested and an explanation was offered for a type of tissue reaction.

**The Etiology of Congenital Malformations in the Light of Biological Statistics.** By Dr. Douglas P. Murphy, Philadelphia, Pa.: Dr. Murphy presented observations on biological and other characteristics of a series of families possessing congenitally malformed children. He gave an evaluation of this material as it helps to explain the cause of congenital defects.

**Sarcoma of Uterus—Clinical and Pathologic Study of Fifty-Nine Cases.** By Dr. Emil Novak, Baltimore, Md.: This paper was based on clinical and pathologic study of 59 cases of uterine sarcoma in a total of 26,973 case specimens in a twenty-five-year period. The series included 2 cases of sarcoma botryoides. Incidence, symptomatology, diagnosis, and end-results were discussed. Of 50 cases traced, 12 were alive and well five or more years; 17 dead within one year after operation; the total five-year salvage was 30 per cent (15 cases). The paper was devoted chiefly to pathologic aspects, with discussion of histogenesis, types, microscopic diagnosis, degrees of malignancy on basis of cell type and mitotic activity, etc. Application of these facts to general principles of treatment was presented.

**The Results of Conservatism in the Treatment of Premature Separation of the Normally Implanted Placenta.** By Dr. Frederick C. Irving, Boston, Mass.: Material: 359 cases from the Boston Lying-In Hospital.

1. External hemorrhage, 240

A. Expectancy, rupture of the membranes, small doses of pituitary extract or dilating bag, 211; 3 deaths, 1.4 per cent

B. Cesarean section, 29 cases; 1 death, 3.4 per cent

Conservative measures give better results for the mother.

2. Internal hemorrhage, 119

A. Pelvic operative delivery, 16 cases; 3 deaths, 18.7 per cent

B. Cesarean section, 69 cases; 10 deaths, 14.5 per cent

C. Conservative measures, 34 cases

Expectancy, 8; rupture of membranes, pack and Spanish windlass, 26 cases, 1 death; rate for conservative treatment, 2.9 per cent

Conservative measures have given  $\frac{1}{6}$  of the mortality of pelvic operative delivery and  $\frac{1}{6}$  of that of cesarean section.

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### Erratum

On pages 570 and 571 of the October issue, in the article by Best and Hicken entitled "A Probable Cause for the High Mortality Following Cholecystostomy-Cholecystogastrostomy, and Cholecystoduodenostomy in Jaundiced Patients," Figs. 2 A and 2 B were printed upside down.



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**The Clinical Significance of Endometrial Hyperplasia.** By Dr. Franklin L. Payne, Philadelphia, Pa.: The statement that endometrial hyperplasia does not necessitate abnormal uterine bleeding is proved in this study. The material consists of 496 premenopausal and 38 postmenopausal specimens of endometrial hyperplasia. Analysis of the premenopausal hyperplasia group shows that abnormal uterine bleeding occurred in 85.2 per cent of the patients, the remainder having normal, scanty, or absent periods. The incidence of hyperplasia in the clinical conditions which are commonly associated with it and the incidence of abnormal bleeding in these conditions are shown. The association of fundal malignancy with both pre- and postmenopausal hyperplasia is discussed. Analysis of the postmenopausal group shows hyperplasia to occur either with or without demonstrable pelvic pathology and often in the absence of uterine bleeding.

**An Unusual Obstetrical Injury, Detaching Bladder and Urethra From the Symphysis Pubis and Causing Complete Epispadias.** By Dr. Guy L. Hunner, Baltimore, Md.: A primipara, aged thirty-eight years, with adequate pelvic measurements, in a spontaneous delivery of an 8.5 pound boy, with R. O. A. position, remained in the second stage of labor sixty-six hours. After complete dilatation of the cervix and spontaneous rupture of the membranes, there was precipitate birth. Dr. Hunner described the injury, particularly to the urethra, as well as the subsequent treatment and results.

**Presidential Address.** By Dr. Fred J. Taussig, St. Louis, Mo.: An excellent résumé of the history of eclampsia, toxemia of pregnancy, and prenatal care.

**Pregnancy Complicated by Ovarian Tumors.** By Dr. Karl M. Wilson, Rochester, N. Y.: Such tumors complicating pregnancy may at times cause no trouble, but more often they are to be regarded as a serious menace. Formerly, the mortality associated with this complication was high, but modern surgical methods have reduced this considerably. The principal dangers lie in abortion, torsion of the pedicle of the tumor, or the production of a mechanical obstacle to labor. A series of twenty-eight cases from the author's service is presented. In this small series all the above complications were noted. The most interesting group in the series is found in those patients where removal of the tumor necessitated removal of the corpus luteum. There is a discussion of the indications and time for operation. There were no deaths in the series.

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## Book Reviews

---

**A Manual of Operating Room Procedures.** By Almira W. Hoppe and Lucile M. Halverson. Pp. 239. Minneapolis, 1937, The University of Minnesota Press. \$2.

This book is a comprehensive, detailed guide with considerable merit for nurses, internes, and surgeons. There is unquestionably a universal need for such a book and it should serve the purpose of reducing the confusion often present in operating rooms in general because of the absence of information arranged in a systematic way. The most commendable part of the book is a brief description of what is to be accomplished, as well as the steps of different operations. This information should be of great value to the nurse, leading to proficiency of a higher degree in the operating room. This particular knowledge should be of great value and applicable to any operating room.

The immense amount of detail as to instruments, sutures, etc., is of value to one particular group of surgeons, but since each surgeon has his own ideas and peculiarities, a more general outline of instruments, equipment, etc., would be of more use to operating rooms in general. An outline indicating the type of instruments, rather than instruments named for some doctor, when possible, would be less confusing.

This is a very creditable book and a very reasonable one. Any operating room would profit by the possession of this guide, which may be and should necessarily have to be modified to conform to local conditions and ideas. It is printed on only one side of the page so that supplementary notes and changes may be conveniently made.

**Wundheilung.** By Wilhelm Löhr. Pp. 234, with 141 illustrations. Leipzig, 1937. Johann Ambrosius Barth. 21 marks.

Texts on the treatment of wounds, it might appear, would be quite unnecessary inasmuch as many of the general surgical texts are written about this central tenet. On the contrary, this fundamental concern of all surgeons is particularly deserving of monographic consideration. When a surgeon analyzes critically his success and failures in the management of acute pyogenic surgical infections, he cannot feel very arrogant over his accomplishments; if he is alive to what his rôle has been, it must occasion in him a sense of true humility.

The author of this text has long had a keen interest in surgical infections and is the author of another text on anaerobic infections. In this monograph, Löhr discusses the various adaptations of the cod liver oil ointment dressings in the treatment of wounds, of which he is the author. All who have tried the method undoubtedly have found some virtue in it. It is difficult to escape the impression, however, that the author credits it more than the method deserves.

The author rightfully stresses the great importance of conservation in the treatment of infections of the extremities. He indorses the Orr treatment of acute and chronic osteomyelitis and discusses in a conservative and orthodox manner the matters of mechanical and chemical cleansing of wounds as well as the place of drainage in the treatment of surgical infections.

This thoughtful consideration of wound management and surgical infections can be enthusiastically recommended to every surgeon for study. Wound treatment, once the chief occupation of the surgeon, merits his continued interest and concern.

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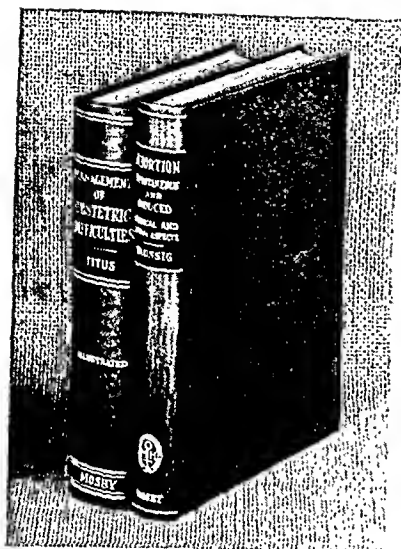
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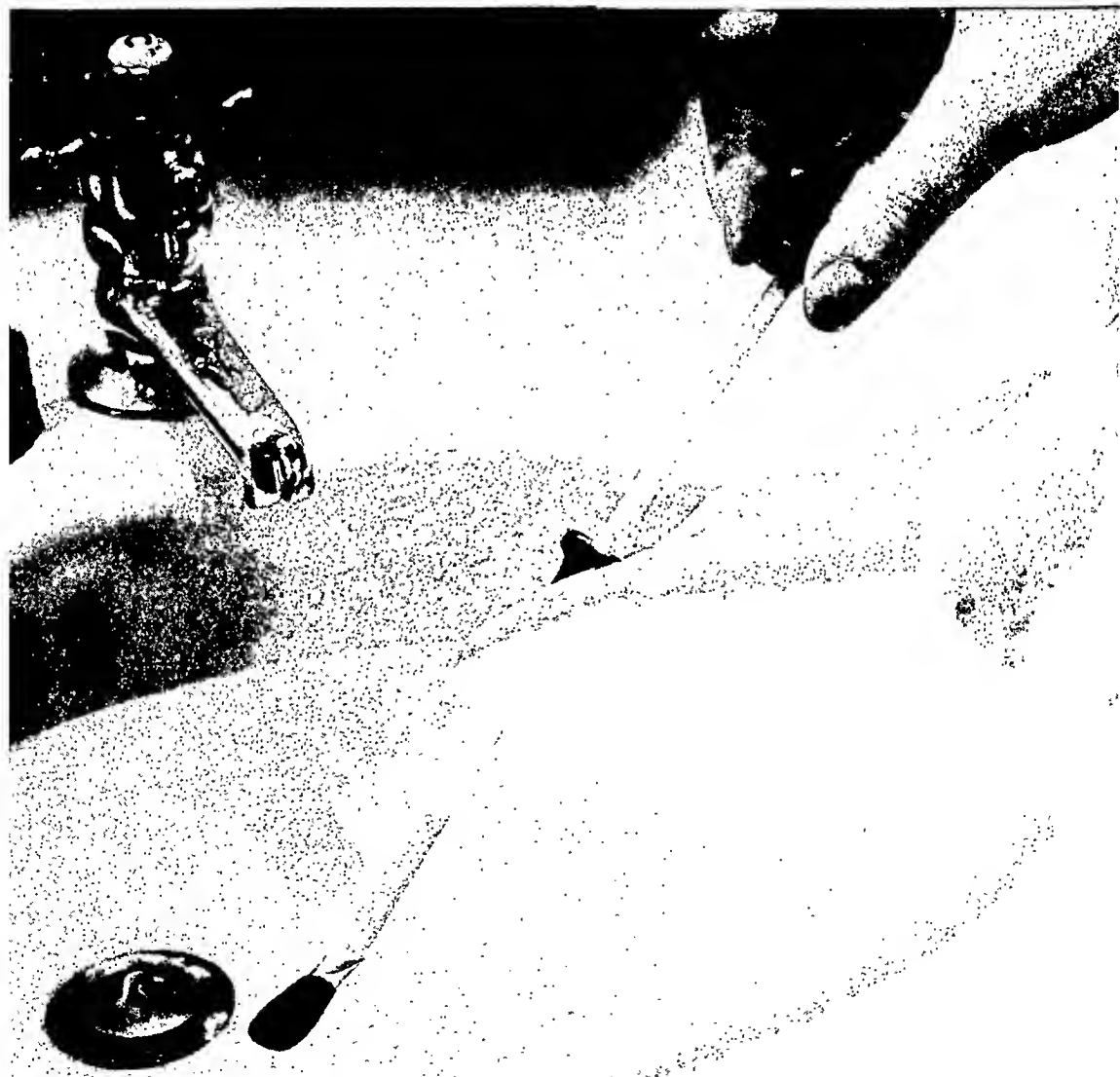
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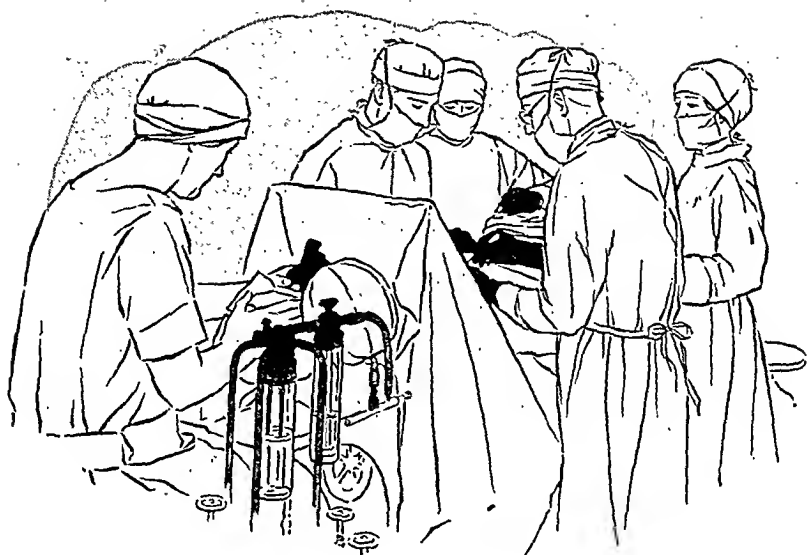
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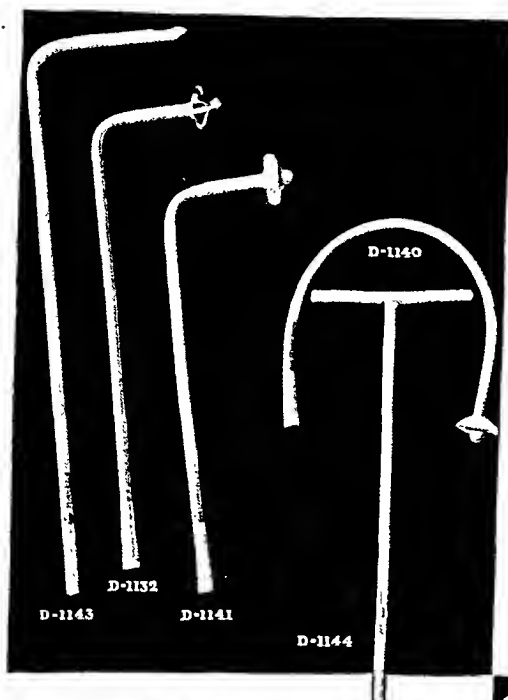
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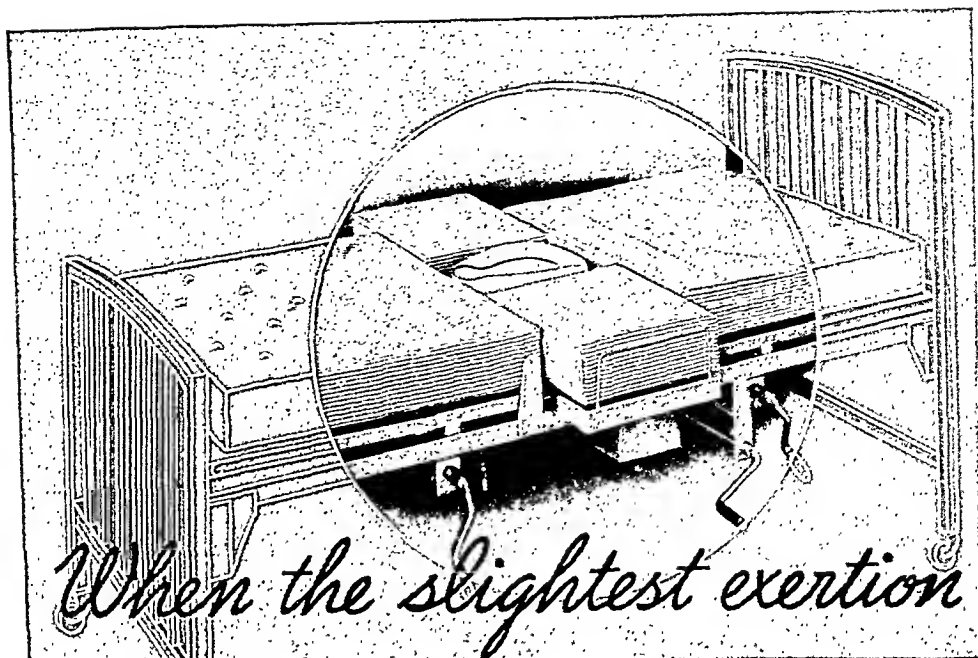
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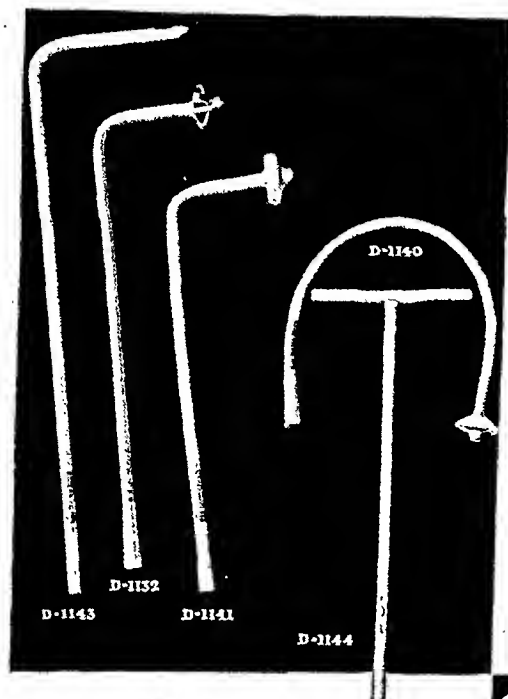
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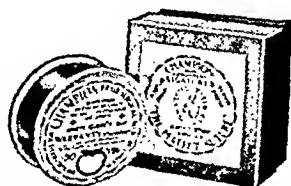
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# SURGERY

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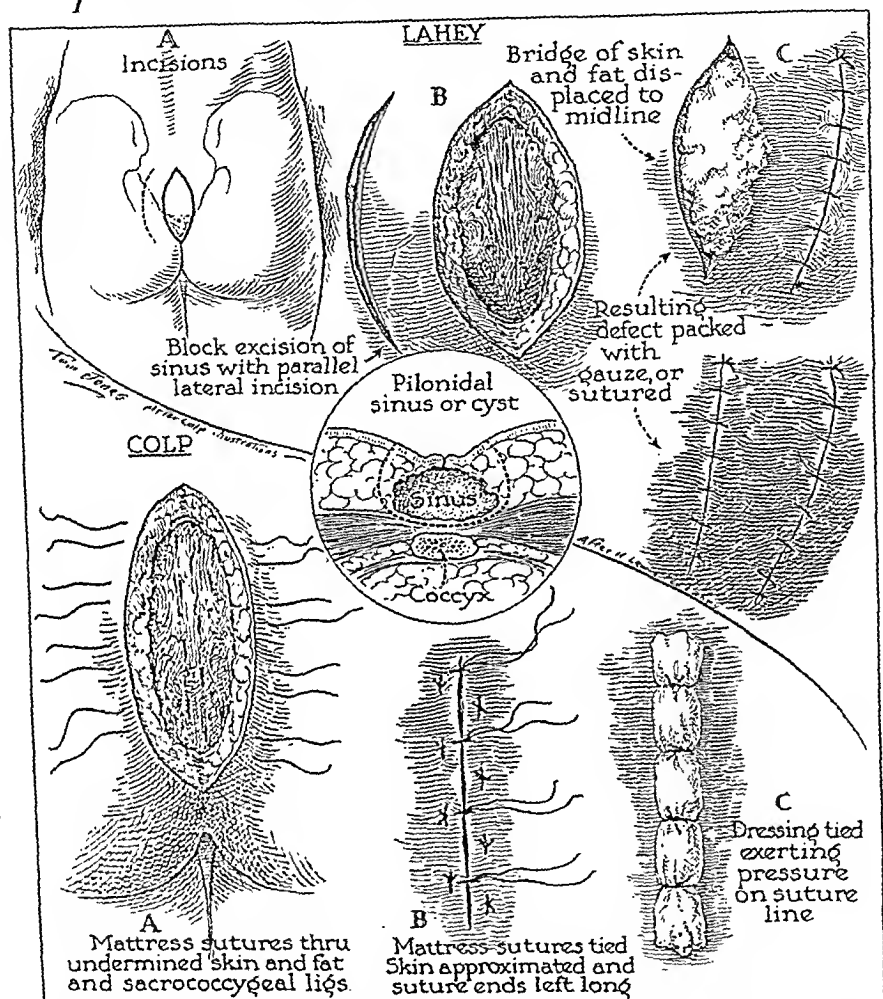
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*Operative Treatment of Pilonidal Sinus*

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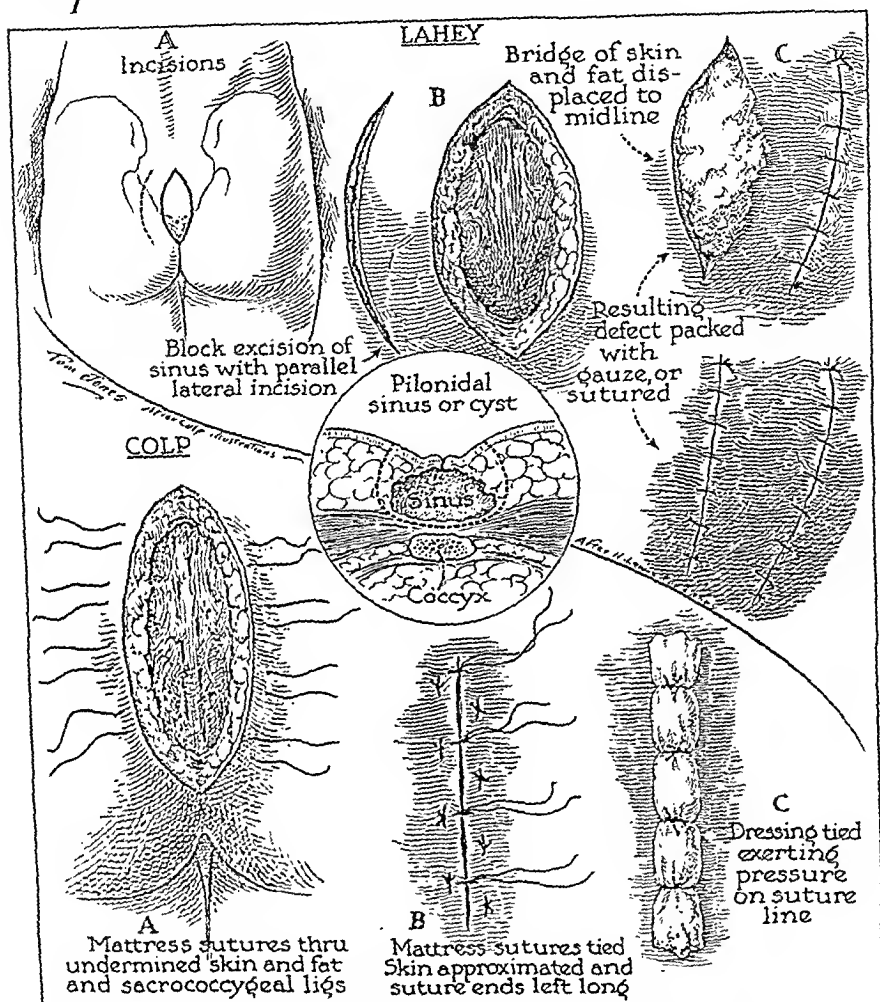
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1543... $\frac{3}{8}$ -Circle Needle.....	A-3.....	4.20
1544...Small $\frac{1}{2}$ -Circle Needle...	A-4.....	4.20
1545... $\frac{1}{2}$ -Circle Needle.....	A-5.....	4.20

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1304...Small $\frac{1}{2}$ -Circle Needle...	A-4.....	4.20
1305... $\frac{1}{2}$ -Circle Needle.....	A-5.....	4.20

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1344...Small $\frac{1}{2}$ -Circle Needle...	A-4.....	4.20
1345... $\frac{1}{2}$ -Circle Needle.....	A-5.....	4.20

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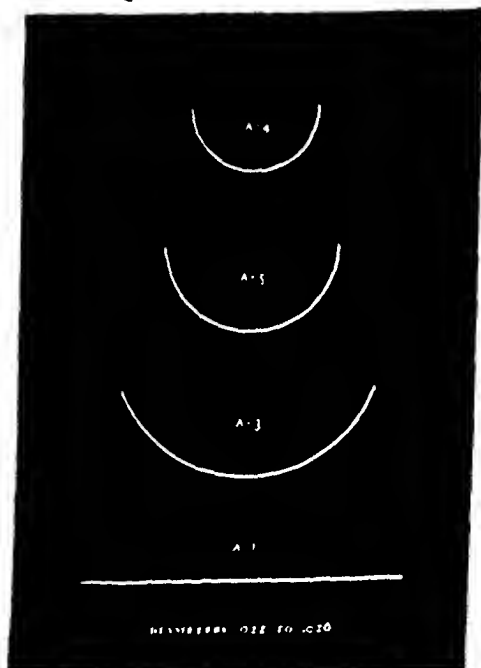
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1352...Two Straight Needles*..	A-1.....	4.20
1354...Small $\frac{1}{2}$ -Circle Needle*..	A-4.....	4.20

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1372...Two Straight Needles*..	A-1.....	4.20
1374...Small $\frac{1}{2}$ -Circle Needle*..	A-4.....	4.20

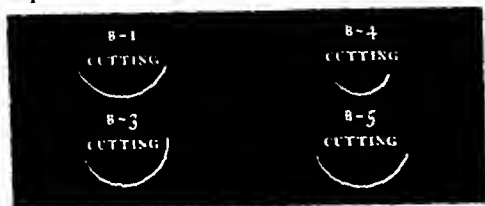
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NO.	MATERIAL	SIZE	NEEDLE
1661...	Black Silk.....	6-0.....	B-3
1663...	Plain Catgut.....	4-0.....	B-5
1665...	Black Silk.....	6-0.....	B-1
1665...	Black Silk.....	4-0.....	B-1
1667...	Plain Catgut.....	3-0.....	B-4
1669...	10-Day Catgut.....	4-0.....	B-5
1669...	10-Day Catgut.....	3-0.....	B-5
1669n...	10-Day Catgut†.....	4-0.....	B-5
1669n...	10-Day Catgut†.....	3-0.....	B-5

### DOUBLE ARMED

1662...	Black Silk *	6-0.....	B-3
1664...	Black Silk *	6-0.....	B-1
1664...	Black Silk *	4-0.....	B-1
1666...	Plain Catgut *	3-0.....	B-4
1668...	10-Day Catgut *	4-0.....	B-5
1668...	10-Day Catgut *	3-0.....	B-5
1668n...	10-Day Catgut†.....	4-0.....	B-5
1668n...	10-Day Catgut†.....	3-0.....	B-5

\* 12 inches † 9 inches

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NO.	MATERIAL	SIZE	NEEDLE
1751...	Kal-dermic.....	00.....	C-1
1752...	Aluminum-Bronze Wire 00.....		C-1
1753...	Black Braided Silk.....	000.....	C-2
1754...	Aluminum-Bronze Wire 00.....		C-4
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1758...	Aluminum-Bronze Wire 00.....		C-3

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NO.	MATERIAL	SIZE	NEEDLE
1635...	Non-Boilable Plain Catgut..	0.....	T-1
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1624...	Black Braided Silk.....	000.....	T-2

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NO.	MATERIAL	SIZE	NEEDLE
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1651...	Kal-dermic.....	6-0.....	B-1
1652...	Kal-dermic.....	8-0.....	B-5
1652...	Kal-dermic.....	6-0.....	B-5
1652...	Kal-dermic.....	4-0.....	B-5
1653...	Black Silkworm.....	4-0.....	B-1
1655...	Kal-dermic.....	4-0.....	B-2
1658...	Black Silk.....	4-0.....	B-2

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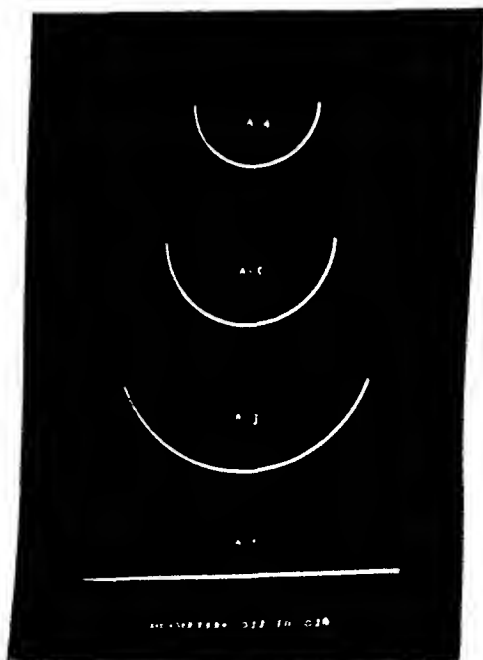
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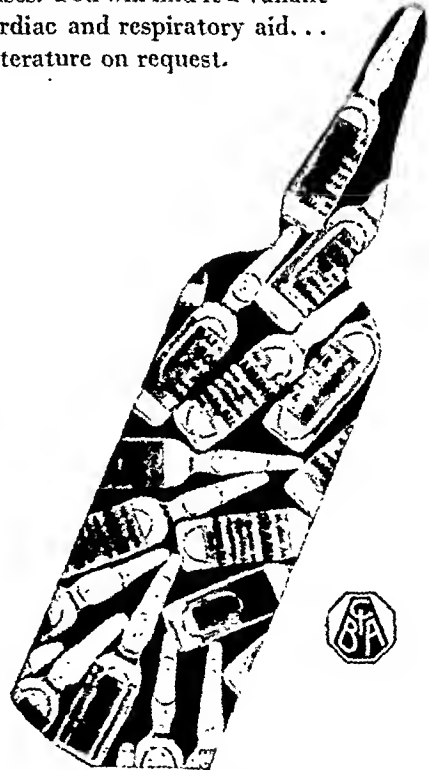
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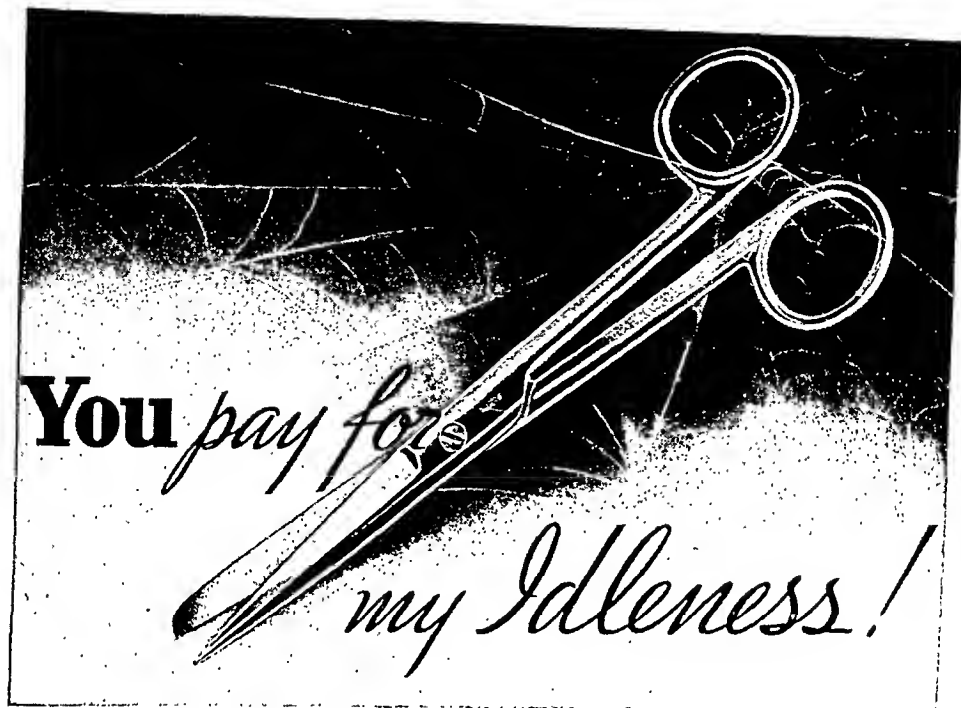
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# SURGERY

VOL. 2

SEPTEMBER, 1937

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## Original Communications

### POPLITEAL ANEURYSMS AS A CAUSE OF PERIPHERAL CIRCULATORY DISEASE: WITH SPECIAL STUDY OF OSCILLOMOGRAPHS AS AN AID TO DIAGNOSIS

FRANK V. THEIS, M.D., CHICAGO, ILL.

*(From the Department of Surgery, Presbyterian Hospital, and the Rush Medical College of the University of Chicago)*

**A**NEURYSM of the popliteal artery is a more important etiologic factor in peripheral circulatory disturbances than is commonly recognized. When the sac is small, definite diagnosis is difficult and the symptoms of intermittent or continuous calf pain and coldness of the foot may overshadow the unusual findings in the popliteal space. As a rule the popliteal space is carefully examined only when serious complications are produced by advanced stages of the aneurysm. Arteriovenous aneurysms, however, are more readily diagnosed. The symptoms and physical findings are more pathognomonic than when the artery alone is involved. The present interest in peripheral circulatory diseases has stimulated more thorough examination, including temperature readings,<sup>1</sup> oscillographs, and differential tests<sup>2</sup> for organic and spastic disease. These studies furnish a more accurate basis for differentiating the causes of peripheral circulatory disturbances.

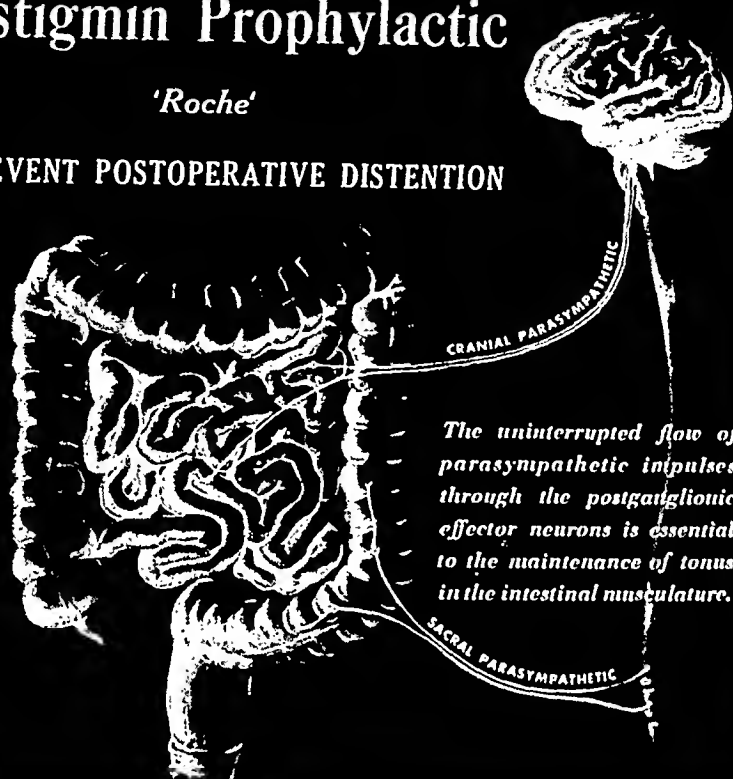
During the past two years, a series of more than 200 patients suffering with peripheral circulatory disease included 5 cases of aneurysm of the popliteal artery. In all 5 cases, the early symptoms were primarily those of peripheral circulatory disease. In 3 of the 5 cases, the sac was patent and the oscillographs were sufficiently characteristic to be confirmatory evidence of the presence of an aneurysm. The height of the oscillations at the site of the aneurysm varies inversely according to vasomotor changes in the distal circulation. When the peripheral temperature readings are low, the oscillogram index is

Received for publication, March 30, 1937.

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to restore early normal peristalsis following laparotomy. Gas pains are greatly diminished if not completely avoided. Nausea, if present, is indirectly reduced in duration." Schlaepfer, "Relief of Postoperative Intestinal Atony with Prostigmin," *The Western Journal of Surgery, Obstetrics, and Gynecology*, July, 1936.

"Our results indicate that prostigmin is of value, both as a prophylactic against and a treatment for paralytic ileus and distention." Uznanski, "A New Treatment for Paralytic Ileus," *Illinois Medical Journal*, December, 1936, 70:567-569.

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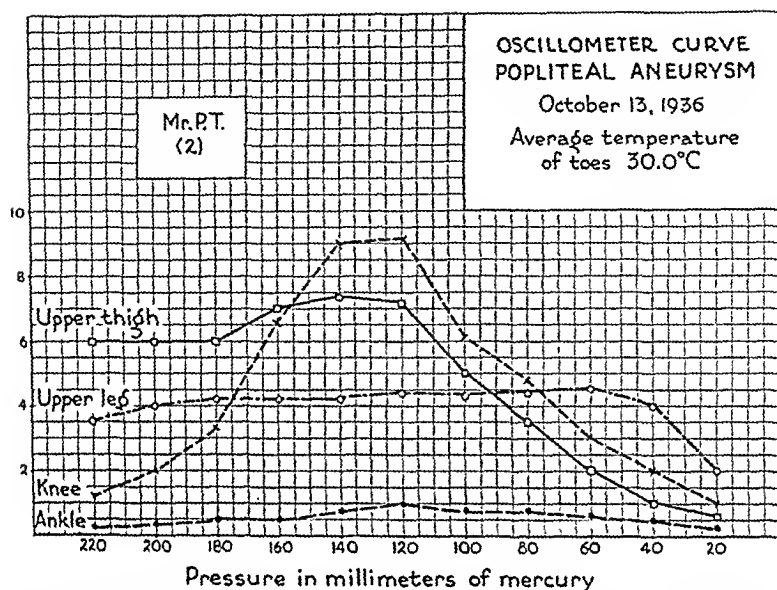


Chart III.—Oscillomographs of same extremity as Chart II (two weeks later) with average temperature of toes of 30.0° C. Note the reduction in the oscillometric index from 13.8 (when the average temperature was 24.0° C.) to 9.1.

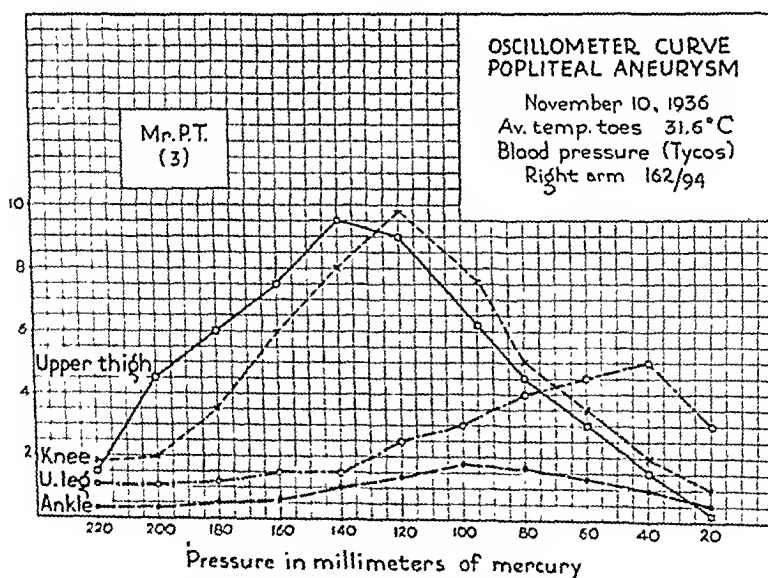


Chart IV.—Same case as Charts II and III with average temperature of 31.6° C. The indices at the upper thigh and knee were both 9.6. With more normal relationship in the height of the curves, the index at ankle has increased also.

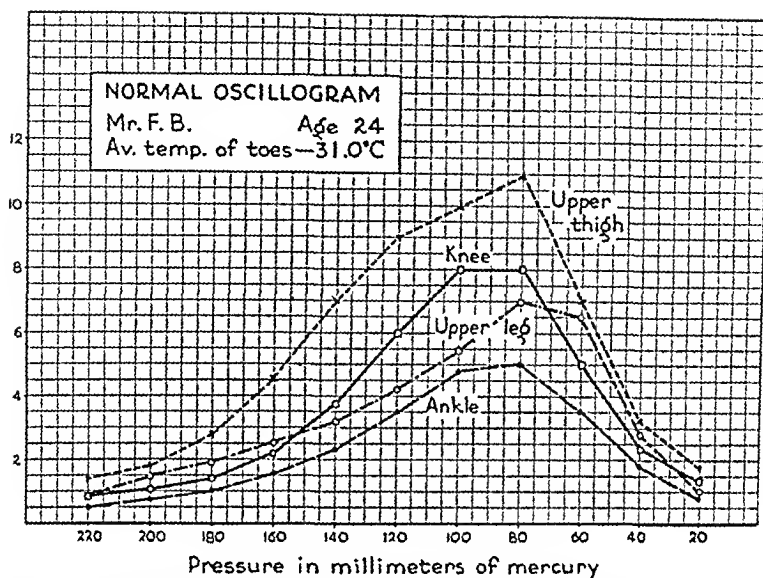


Chart I.—Normal oscillogram. The curves were made from oscillographic readings obtained from the upper thigh, knee, upper leg, and ankle. Note the distal reduction in the oscillographic index (height of the curve) at the different levels. The average temperature of the toes (stabilized) was 31.0° C.

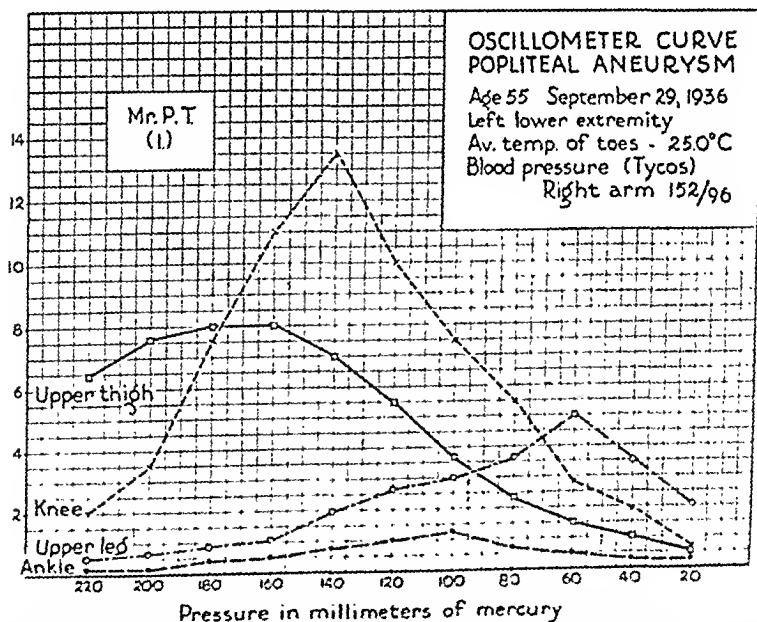


Chart II.—Oscillogram of popliteal aneurysm described in Case I. An oscillographic index of 13.8 at the knee was obtained when the average temperature of toes was 25° C. Note the relation of the curves from the various levels of the extremity.

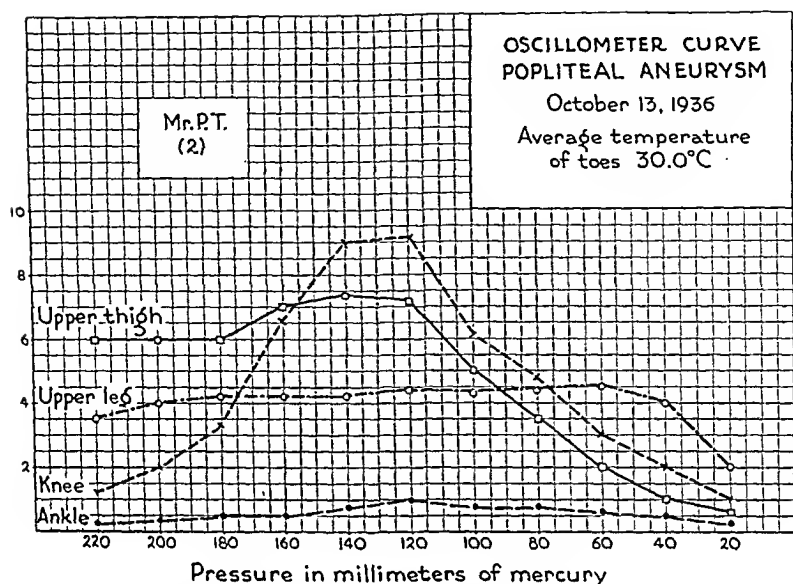


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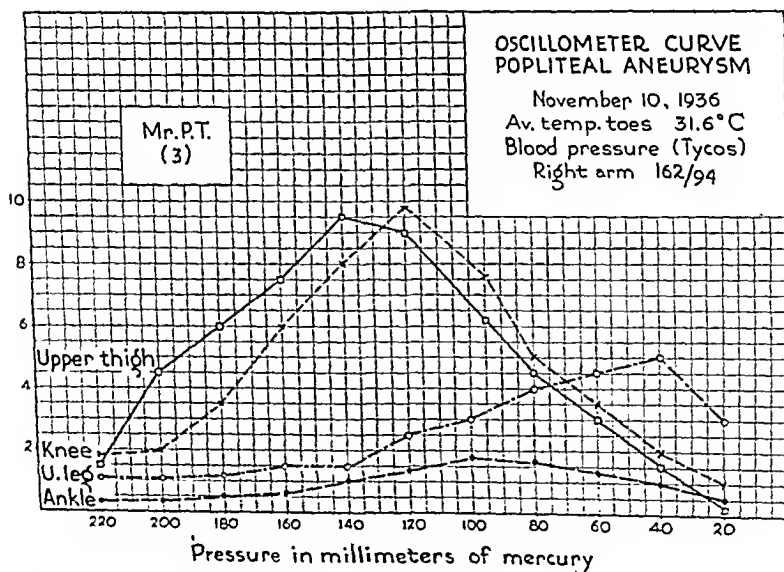


Chart IV.—Same case as Charts II and III with average temperature of 31.6° C. The indices at the upper thigh and knee were both 9.6. With more normal relationship in the height of the curves, the index at ankle has increased also.



high. After return of normal temperature readings, the index is again reduced. These observations suggested a review of all oscillometric records, especially those with undiagnosed causes of peripheral circulatory disease.

#### REPORT OF FIVE CASES

CASE 1.—Mr. P. T., aged fifty-six years, an engineer, had no symptoms referable to his legs until five years prior to examination. At that time while in a squatting position, working in his garden, he lost his balance. A violent muscle strain at the knee prevented his falling. Simultaneously he suffered severe pain in the back of the left knee. The pain persisted for the remainder of the day but by the next morning had completely disappeared. Periodically, since then, he has suffered disabling attacks of severe cramps in the calf muscles and coldness of the foot. Medical opinion had differed as to the presence of an aneurysm.

On admission to the Presbyterian Hospital, September 29, 1936, a definitely expansile egg-shaped firm tumor was palpable in the lower part of the popliteal space. Peripheral toe temperatures on the left foot averaged  $25^{\circ}\text{C}$ ., while on the right foot they averaged  $30.2^{\circ}\text{C}$ . The oscillometer readings (Chart II) were the findings of a popliteal aneurysm. Return of normal peripheral temperatures was accompanied by almost normal oscillometer readings (Charts III and IV). Wassermann test was negative.

On November 16, 1936, after walking rapidly a distance of seven blocks, severe cramps recurred in the left calf muscles. These cramps were so severe that he was completely incapacitated. The foot became cold and the entire leg painful. He had previously experienced the same difficulty when walking hurriedly. The symptoms gradually but completely subsided within one week. During this period the foot remained cold and the oscillometer index at the knee again showed increased oscillations.

*Comment.*—This case illustrates the relation of deficient peripheral circulation to the amplitude of oscillations in an aneurysm. With decreased peripheral circulation (evidenced by lower temperature findings, reduced oscillometer index, coldness to touch, and intermittent claudication), the oscillations in the popliteal aneurysmal sac were greatly increased. With improvement in peripheral circulation (decreased peripheral resistance to the flow of blood), oscillations in the aneurysmal sac were again reduced.

CASE 2.—Mr. E., a policeman, aged fifty-two years, had been incapacitated for ten years because of intermittent claudication, continuous rest pains in the calf muscles, and coldness of the feet. The symptoms had become progressively worse until at the time of admission to the Presbyterian Hospital, November 5, 1935, he was only able to walk one block without resting before continuing. Temperatures of the left toes, determined with a thermocouple, averaged  $24.6^{\circ}\text{C}$ ., and that of the right toes averaged  $24.3^{\circ}\text{C}$ . Arm blood pressure was 168/110. The oscillometric index at the right knee was 20 (Chart V) and at the left knee 13. With return of normal peripheral temperature readings ( $30.6^{\circ}\text{C}$ .) the index at right knee was 13 (Chart VI). As the peripheral circulation was again reduced (temperature readings of  $27^{\circ}\text{C}$ .) the oscillometric index at the knee rose to 16. A definitely expansile tumor was palpable in each popliteal space. Repeated Wassermann tests were negative.

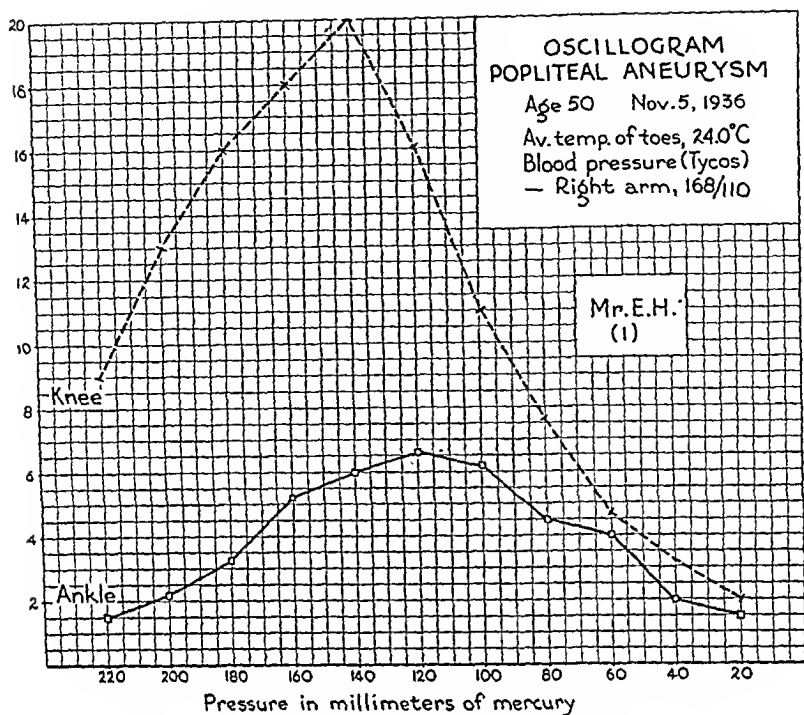


Chart V.—Oscillograph of Case 2. An index of 20 at the knee was obtained when the average temperature of toes was 24.0° C.

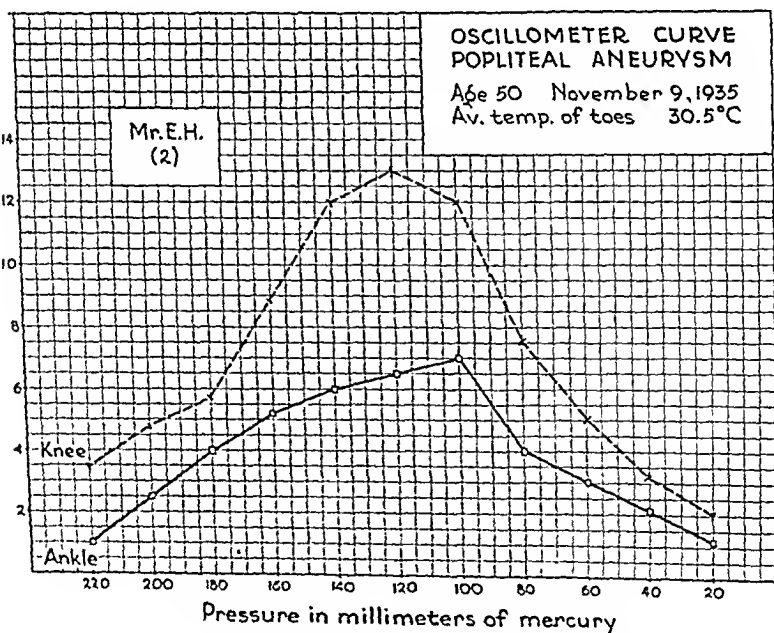


Chart VI.—Same case as Chart V showing an index of 13, when the average temperature of toes was 30.5° C.

*Comment.*—The relation of peripheral circulation to the oscillometric index at the knee is again illustrated. With each recurrence of deficient circulation in the toes, the oscillometer readings in the popliteal space were increased. Normal peripheral circulation was accompanied by a marked reduction in oscillations. No thrombosis or pressure symptoms occurred.

CASE 3.—Mr. A. L., aged sixty-one years, a clerk, had symptoms of intermittent claudication for about six years prior to admission January 23, 1935. Cramps in both legs became progressively more disabling until as much as five minutes' complete rest was required after walking one city block. Three months previous to ex-

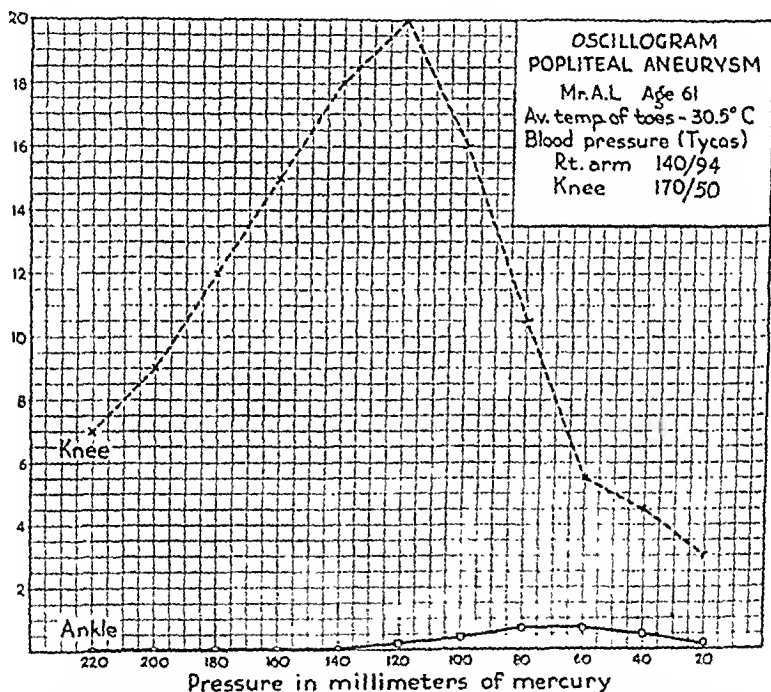


Chart VII.—Oscillograph of popliteal aneurysm described in Case 3. The average temperature of the toes of 30.5° C. (stabilized for 1 hour in temperature-controlled room at 20° C.) with almost zero oscillometric index at the ankle indicated the adequacy of collateral circulation. At the level of the aneurysm the oscillometer index was 20.

amination while he was sitting at home he developed a sudden excruciating pain in the right leg and foot. The foot immediately became cold, pale, and continuously painful. All peripheral arterial pulsations were absent. Gradually the toes became gangrenous and infected which necessitated amputation. Thigh and ankle oscillometer readings were zero. Wassermann test was negative.

The peripheral temperature readings on the left leg at the time of the initial examination were almost normal. The average temperature of the toes in a temperature-controlled room at 20° C. was 30.6° C. In spite of these findings, intermittent claudication had been as severe as in the right leg for more than six years. Oscillometric index at the knee was 20 and at the ankle 0 (Chart VII).

Examination of the left popliteal space revealed an egg-sized, soft expansile swelling. Arm blood pressure was 140/90. Blood pressure (Tycos sphygmomanometer) at the knee was 170/50 and the oscillometric index was 20. While convalescing from the right leg amputation, the swelling in the left popliteal space gradually became hard and pulsations ceased. The foot rapidly became gangrenous.

*Comment.*—The aneurysm of the left popliteal artery produced symptoms of peripheral circulatory disease for six years. Although unrecognized until the oscillometer readings suggested its presence,



FIG. 1.—Small area of infected gangrene at base of first toe nail described in Case 4. Although symptoms of far-advanced peripheral circulatory disease were present for months, gangrene did not develop until infection set in after cutting the toe nail. The two popliteal aneurysms and the popliteal artery (Fig. 2) were completely thrombosed.

thrombosis with acute circulatory deficiency did not occur until amputation of the right leg required prolonged convalescence.

CASE 4.—Mr. O. T., aged eighty years, was referred September 22, 1936; with severe senile arteriosclerotic circulatory disease of the left foot. There was a small area of infected gangrene at the base of the first toe nail (Fig. 1), and the entire dorsum of the foot and all the toes were discolored and painful. Extreme continuous rest pains had been present for only two weeks, but limitation in walking because of calf pains and coldness of the foot had been troublesome for some months. While taking a long walk three months previously, he developed an unusually severe attack of pain in the calf of the left leg. From this time on deep blue red,

*Comment.*—The relation of peripheral circulation to the oseillometric index at the knee is again illustrated. With each recurrence of deficient circulation in the toes, the oseillometer readings in the popliteal space were increased. Normal peripheral circulation was accompanied by a marked reduction in oscillations. No thrombosis or pressure symptoms occurred.

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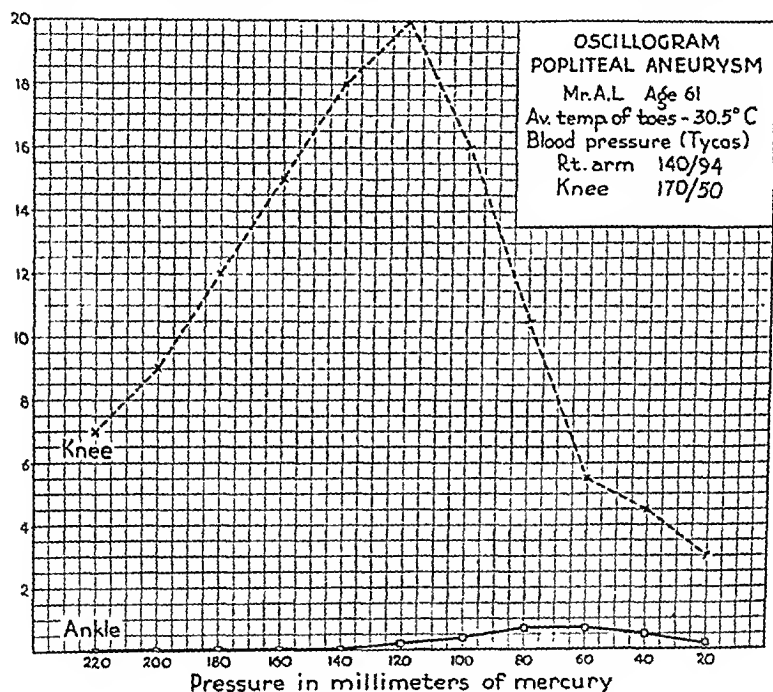


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dependent discoloration of the foot and toes, coldness of the extremity, rest pains, and intermittent claudication became progressively more severe. Although the disease was far advanced, he still continued to be moderately active until his admission to the Presbyterian Hospital.

On admission to the hospital there was complete absence of pulsation in the dorsalis pedis, posterior tibial, and popliteal artery on the left side. Good pulsation was present in the femoral artery. The oseillometer readings were zero at the ankle and 1.5 at the knee. In the dependent position the toes and foot were a deep blue red and cold. With the leg elevated the deep discoloration of the foot quickly

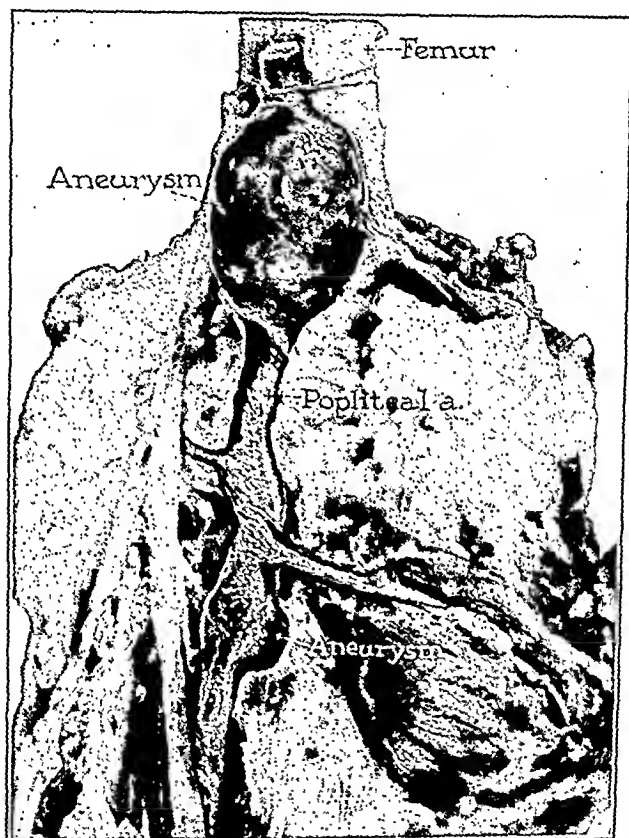


Fig. 2.—Photograph of dissected popliteal space from amputation specimen shown in Fig. 1. Note the two aneurysms and the enlarged collateral arteries.

disappeared, but a bright red hyperemie flush persisted. The surface temperatures of the toes and foot averaged  $27.5^{\circ}\text{C}$ ., while on the right foot the average was  $30^{\circ}\text{C}$ . X-ray examination revealed moderate sclerosis of the vessels of both legs. Mouth temperature fluctuated between  $99^{\circ}\text{F}$ . and  $100^{\circ}\text{F}$ . Wassermann test was negative.

Because of the infected gangrene, cellulitis of the foot, and condition of the peripheral circulation, midhigh amputation was performed September 24, 1936. Examination of the operative specimen revealed two sacular popliteal aneurysms (Fig. 2) with laminated thrombi and a thrombus in the popliteal artery which

extended for about 1 cm. into the femoral artery. The posterior and anterior tibial arteries were slightly sclerosed but not thrombosed.

*Comment.*—Complete occlusion of the aneurysms and popliteal artery did not produce extensive gangrene. It is probable that the intermittent claudication and coldness of the foot which existed for some months were due to the patent aneurysms. The onset of continuous severe pain in the foot occurred at the time of infection. In spite of the patient's advanced age he was not totally disabled by either the aneurysms or thrombosis of the popliteal artery. With the popliteal artery completely occluded, the oscillometric reading at the knee of 1.5 was evidence of the slowness of the arterial occlusion which permitted time for the collateral arteries to enlarge.

CASE 5.—Mr. A., aged forty-six years, a contractor, had received intensive anti-syphilitic treatment some years previously but otherwise enjoyed good health. Fifteen months prior to examination, he tripped while bowling. Following extreme muscular effort to prevent falling, a severe pain immediately developed in the back of the right knee. This persisted for a few days and completely disappeared so that he continued his normal daily activity without discomfort or disability. Three months previous to examination (one year after initial injury) without warning the leg suddenly became cold, pale, and painful. Severe cramps occurred in the calf muscles especially when attempting to walk rapidly (intermittent claudication). At no time had he been completely incapacitated. A hard, egg-sized, nonpulsating tumor mass was palpated in the right popliteal space. There was complete absence of pulsation in the popliteal, posterior tibial, and anterior tibial arteries and coldness of the foot and leg.

On October 6, 1936, the right foot and leg appeared no different than the left. However, a hard, nonpulsating swelling was palpable in the right popliteal space and peripheral pulsations were absent, while on the left side all pulsations were palpable. The oscillometric index at the right ankle was almost zero. In the thigh above the tumor an index of 12 was recorded. All readings on the opposite side were increased above normal with 13.5 at the level of the lower thigh. Surface temperatures: 27.5° C. on the right side and 26.4° C. on the left side. Considerable subjective improvement followed elevation of skin temperatures under treatment.

*Comment.*—A palpable thrombosed aneurysm with absence of all peripheral pulsations was accompanied by neither trophic disturbances nor marked limitation in movement. Collateral arterial channels provided sufficient circulation. The syphilitic history might have suggested syphilitic endarteritis had not the palpable solid tumor and etiology of severe muscular strain at the knee been so pathognomonic.

#### DISCUSSION

*Mechanism.*—Aneurysms of the popliteal artery produce disturbances in peripheral circulation even before the onset of local symptoms in the popliteal space. With the arterial pressure at least partially expended in dilating the aneurysmal sac, a corresponding reduction in pressure occurs in the distal circulation. Accordingly, the peripheral arterial pulsations and temperature readings are reduced. By pre-



venting expansion of the aneurysmal sac with direct pressure, there is improvement in the peripheral circulation.<sup>3</sup> This can be likened to a long rubber balloon with a saccular or fusiform weakened area. In expanding such a balloon, the dilating pressure will be spent in the weakened area at the expense of the proximal and distal portion. Conversely, increased peripheral resistance to the flow of blood due to muscular activity or to vasoconstriction from exposure to cold will be accompanied by greater dilatation of the aneurysmal sac. This is well illustrated by the oscillograms and peripheral temperature readings in the cases herewith reported.

*Frequency.*—The published reports in the literature are of little value in estimating the frequency of popliteal aneurysms as the cause of peripheral circulatory disease. Generally a diagnosis of aneurysm is made only when the sac is large and (a) a definitely expansile tumor is palpable;<sup>4</sup> (b) when pressure on the adjacent nerves, veins, or joint gives rise to local pain, swelling, or disability;<sup>5</sup> (c) when thrombosis of the sac forms a palpable solid tumor or simultaneous thrombosis of the popliteal artery results in acute peripheral circulatory deficiency;<sup>6</sup> (d) and when the sac ruptures into the knee joint or the surrounding tissues.<sup>7</sup> By the time these complications occur, surgical intervention is usually necessary. Consequently most reports are surgical.

The classical publications on aneurysms, written more than twenty-five years ago, are still the outstanding contributions on the subject. Matas<sup>8</sup> collected reports on 106 surgical aneurysms, covering all the important regions of the body, 62, or 58 per cent, of which were of the lower extremity. Of these 62 cases, 66.4 per cent were of the popliteal artery. Delbet,<sup>9</sup> in 1897, reported on a series of 358 cases of popliteal aneurysms. Autopsy statistics cannot be used since the extremities are rarely included in the dissections. The available statistics are, therefore, of little value in estimating the relative frequency of smaller unoperated as well as the surgically demonstrated popliteal aneurysms as the cause of peripheral circulatory disease. There is no doubt, however, that peripheral aneurysms occur most frequently in the popliteal artery.

Early diagnosis of popliteal aneurysm on local physical findings only is usually difficult. The artery lies deep in the popliteal space and is covered by dense tissue and by the tense popliteal fascia. As a rule, slight flexion and relaxation of the muscles of the knee facilitate palpation of normal arterial pulsation, although even in this position deep digital pressure is necessary.<sup>10</sup> With a patent aneurysmal sac the pulsation is more prominent, but the expansile character or size of the dilatation cannot always be detected because of the tense fascial covering. Furthermore, the bruit or murmur so frequently described as pathognomonic was not present in any of the cases herein reported.

## INTERPRETATION OF OSCILLOMOGRAPHS

When the diagnosis is uncertain, oscillomographs may be of help in confirming the presence of an aneurysm. Normal oscillometer readings with distal reduction (Chart I) are: thigh, 4 to 16; upper leg, 3 to 12; and ankle, 1 to 10.<sup>11</sup> At the site of local expansile dilatation of the artery there should be an increased oscillometric index. In reviewing the oscillomographs of more than 200 patients suffering with peripheral circulatory disease, 26 had readings at the knee above the normal 12 units of oscillations. Of these, 9 were on the right side; 6 were on the left side; and 5 were bilateral. This might be accepted to confirm Matas' observation that there is frequent bilateral occurrence of aneurysms of the popliteal artery. Still, I do not believe that an increased reading alone justifies diagnosis of aneurysm. The systemic blood pressures and the vasomotor tone and elasticity of the entire arterial segment must be considered. Friedlander,<sup>12</sup> after studying more than 500 oscillomographs, concludes that the height of the curve is not as important as the form of the graph.

The oscillometric curves herewith illustrated show three distinctive features at the site of the aneurysm: (1) increased height of the curve above the normal limits; (2) absence of normal distal reduction in the height of the curves from the thigh to the ankle; (3) fluctuation in the height of the curve as a result of peripheral vasoconstriction or vasodilatation. The graphs show that oscillometer readings as high as 20 were obtained where ordinarily 3 to 12 is considered normal. Instead of normal distal reduction, Case 1 shows readings at the knee which are 50 per cent greater than at the level of the upper thigh. Furthermore, as shown in Charts II to VI inclusive, distal vasoconstriction (low temperature readings of foot) is accompanied by greatly increased oscillations at the knee. Following release of vasoconstriction (increased peripheral temperatures) the oscillometer readings at the knee were reduced. These observations seem to be sufficiently distinctive to be of help in confirming the diagnosis of peripheral aneurysm. A survey of the literature has been of little assistance in interpreting these observations. For the most part the published reports on oscillomographs deal with interpretations of findings in organic occlusive arterial disease.<sup>13</sup>

## ETIOLOGY

Popliteal aneurysms are rarely produced by direct trauma to the artery. Matas<sup>8</sup> observed that when a history of onset is given violent muscle strain or effort which increases arterial tension precedes the initial symptoms. Similarly, Delbet<sup>9</sup> noted that forceful flexion of the leg obstructs the popliteal artery and sudden violent contraction of the muscles raises the blood pressure in the collapsed artery. Rupture of the two inner coats of the vessel results. If the rupture is small, the

aneurysm is slow in forming. A history of violent muscular strain while the knees were flexed is given in Cases 2 and 4 of the present series. That almost all these aneurysms occur in men might be due to the violence of muscular effort.

Syphilis is known to be an etiologic factor in aneurysms, especially those of the aorta. Since the disease attacks the media of the artery, a weakening of the arterial wall may preexist. All the cases in the present series had negative Wassermann tests, although in one case there was a history of syphilis. Delbet's thorough report questions whether popliteal aneurysms are proportionately more frequent in syphilitics, although he noted a greater frequency of aneurysms in Japan where syphilis is more prevalent. He also found that syphilis occurs equally in the army and navy, while these aneurysms are more frequent in soldiers than in sailors. However, syphilis has not been established as an important etiologic factor in the occurrence of popliteal aneurysms.

Occupation may contribute not only to the formation but also to the enlargement of popliteal aneurysm. In Matas' series as well as in Delbet's series of surgical popliteal aneurysms, mostly the laboring class was affected, while, on the contrary, in the series herewith presented none of the patients were of the laboring class. It was noted in the latter case histories and charts that strenuous exercise and exposure to cold produced a marked increase in the oscillations within the patent aneurysmal sac. Naturally the laboring class is subjected to great muscular effort and exposure to cold which may contribute to the rapid development of surgical aneurysms. It is possible that enlargement of the sac may be delayed by avoiding severe muscular exercise or exposure to cold.

#### ARTERIOGRAPHY

Arteriograms have recently been recommended as an aid in diagnosing and locating popliteal aneurysms. Although Berberich and Hirsch (1923)<sup>14</sup> were the first to use arteriography on living humans, Demel, Sgalitzer, and Kollert (1931),<sup>15</sup> of Vienna, were the first to report thoroughly on the procedure in peripheral circulatory disease. Their experience in 40 cases of arteriosclerotic disease did not include aneurysms. Fontaine and Maitre,<sup>16</sup> Allen and Camp,<sup>17</sup> and others<sup>18</sup> have made similar investigations. Leriche and Arnuft<sup>19</sup> and Barker<sup>20</sup> have reported on the value of arteriography in popliteal aneurysms. A surgical incision of the thigh for isolation of the femoral artery is necessary to inject the roentgen contrast solution.<sup>21</sup> The objections to an intraarterial injection<sup>22</sup> make one hesitant in using this procedure, although in selected cases, especially when multiple aneurysms<sup>23</sup> are suspected, arteriography is the only means of visualizing the exact pathology.

## THEIS: POPLITEAL ANEURYSMS

TABLE I  
ANEURYSM OF THE POPLITEAL ARTERY; SUMMARY OF CASES

CASE	AGE	SEX	OCCUPATION	EX- TREMITY	CAUSE	DURATION PERIPHER- AL CIRCUL- ATORY DIS- TURBANCE	LOCAL FINDINGS POPLITEAL SPACE	PERIPHERAL ARTERIAL PULSATION			GANGRENE	SYPHILIS	
								DP	PT	POP		III- TORY	WASS.
1	56	M	Engineer	Left	Forced flexion; violent muscle action	5 yr.	Large, pulsating tumor	0	0	+++	None	No	Neg.
2	52	M	Policeman	Bilateral	Unknown	10 yr.	Pulsating swelling	++	++	+++	None	No	Neg.
3	61	M	Clerk	Left	Unknown	6 yr.	Pulsating swelling	0	0	+++	Toes and foot	No	Neg.
4	80	M	Merchant	Left	Unknown	1 yr. or more	Pulsating swelling	0	0	0	Infection side of first toe.	No	Neg.
5	46	M	Contractor	Right	Forced flexion; violent muscle action	15 mo.	Firm, nonpulsating tumor	0	0	0	None	Yes	Neg.

## PROGNOSIS

Spontaneous cure by thrombosis of the aneurysmal sac has been observed, but there is the danger of complete occlusion of the popliteal artery, the most serious result of which is gangrene of the toes or foot. However, in 3 of the 5 cases reported, thrombosis of the sac and the popliteal artery produced neither trophic disturbances nor severe disability. The adequacy of collateral circulation depends to a large extent upon the rapidity of the occlusion. In the presence of poor circulation, infection is a most serious complication and led to gangrene in 2 cases. Recent advance in the treatment of peripheral circulatory diseases has improved the prognosis in popliteal artery obstruction. During the past two years I have observed 7 additional extremities with popliteal artery occlusion. In 5 cases, adequate treatment with positive and negative pressure<sup>24</sup> resulted in complete clinical recovery. The 2 cases which were not treated by this method developed extensive gangrene.

## SUMMARY AND CONCLUSIONS

Five cases of aneurysm of the popliteal artery in which the primary symptoms were those of peripheral circulatory disease are herewith reported.

Early diagnosis of popliteal aneurysm on local findings only is usually difficult. In the absence of local symptoms in the popliteal space, the presence of an aneurysm may be overlooked. Examination for all peripheral circulatory diseases should include temperature readings, oscillographs, and differential test for organic and spastic disease.

Oscillographs as herewith illustrated seem to be sufficiently distinctive to be used in confirming diagnosis of aneurysm. The three features of the curves at the site of the aneurysm are: (1) increased height above the normal limit; (2) absence of normal distal reduction in the height of the curves from the thigh to the ankle; (3) fluctuation in the height of the curve as a result of peripheral vasoconstriction or vasodilatation.

Strenuous muscular exercise or vasoconstriction in the foot and leg as a result of exposure to cold were found to be associated with greatly increased oscillations in the aneurysmal sac. This may explain the reported greater frequency of large surgical aneurysms in men who do heavy laboring work. All five cases herewith reported were men whose occupation did not require heavy work, although in two cases violent muscular effort was accidentally incurred. The other three patients had no knowledge of the time of onset of the aneurysms or of the peripheral circulatory disease. Indirect trauma, the result of forced flexion of the knee and violent muscular strain, appears to be

the most important cause of popliteal aneurysm. This was noted by Delbet more than forty years ago.

Spontaneous thrombosis of the aneurysm and popliteal artery may cause gangrene of the extremity. In 3 of the 5 cases that I have reported, arterial obstruction occurred but resulted in gangrene in only 1 case. In this case gangrene developed during prolonged convalescence following amputation of the other extremity.

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# THE DISTRIBUTION OF ANHIDROSIS FOLLOWING INTERRUPTION OF VARIOUS SYMPATHETIC PATHWAYS IN MAN\*

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(From the Mayo Foundation)

THE sweat glands are innervated by the thoracolumbar or sympathetic division of the autonomic nervous system. The spinal centers for innervation of the sweat glands of the head, neck, upper extremity, and upper portion of the thorax are between the eighth cervical and the sixth thoracic segments. The preganglionic portions of these upper thoracic segments are distributed mainly to the upper thoracic and cervical ganglions. From these ganglions the secretory nerve fibers join the peripheral nerves by way of the gray rami communicantes and arrive at the sweat glands by way of the cutaneous nerves. The spinal centers for the lower part of the trunk and lower extremities are between the sixth thoracic and upper lumbar segments. The preganglionic fibers pass to the ganglions of the sympathetic trunks. From these ganglions the secretory nerve fibers join, by way of the gray rami communicantes, the spinal nerves and are distributed peripherally through the cutaneous branches of these nerves. The sympathetic secretory nerve fibers are intimately associated with the sympathetic fibers to the peripheral arterial system, the sebaceous glands, and the pilomotor muscles.

A method for determining the distribution of the secretory nerve fibers to the sweat glands of man was made possible by the advent of surgical procedures on the sympathetic nervous system for peripheral vascular disease.<sup>1, 2</sup> As other clinical conditions, such as essential hypertension,<sup>3, 4, 5, 7, 12</sup> became amenable to treatment to surgical interruption of the vasomotor pathways, study of the distribution of the secretory nerves to the sweat glands was enlarged in scope. In this work, the surgical operations were performed by Adson and Craig, using the procedures especially developed by them. The extent of the surgical procedures will be described in detail in the section on material.

In man, sweating produced by heating the body indicates the presence of sympathetic secretory fibers.<sup>8</sup> The response occurs as a reflex, mediated through the central nervous system and the sympathetic

\*Abridgment of thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Read before the meeting of the American Physiological Society, Memphis, Tenn., April 21 to 24, 1937.

Received for publication, March 10, 1937.



nerve supply to the sweat glands. Whenever the vasomotor pathways to a given cutaneous area are interrupted, sweating in that area, induced reflexly by heat, ceases permanently.<sup>8</sup> I wish to present in this paper the distribution of anhidrosis following interruption of various sympathetic pathways.

#### METHODS

In the method<sup>11</sup> used to determine the presence or absence of sweating, heat and calorimetry were employed. Determinations were based on the chemical fact that cobaltous chloride, in a saturated alcoholic solution, is deep blue but turns to bright pink on the addition of water. The patient is stripped; a small amount of this saturated solution is applied over the parts in which the presence or absence of sweating is to be determined. A small brush is used and the solution is either dotted on the skin or applied in stripes. The skin dries readily if the solution is put on in small quantities. To produce sweating, an aluminum heat cabinet large enough to cover the entire body and containing a series of incandescant globes is placed over the patient. A temperature of 130 degrees F. to 140 degrees F. is maintained until sweating has been induced. If sweating is delayed, a hot drink will hasten its appearance. The heat cabinet is then removed and the portions of skin to which the solution has been applied are observed immediately. Where sweating has occurred, the dots or stripes of solution are bright pink. In places where varying degrees of sweating can be observed, the transition can be noted with considerable accuracy by the change in color of the stripes. On humid days, sufficient moisture may be present in the air to effect a change in color of the solution, but it is never the deep pink observed in the presence of sweating. Furthermore, the heat cabinet eliminates the factor of atmospheric moisture.

In a few cases, in addition to use of the above mentioned method, pilocarpine hydrochloride was used;  $\frac{1}{10}$  to  $\frac{1}{2}$  grain (0.006 to 0.013 gm.) was given intramuscularly and without the use of heat. These tests were made at various intervals following the surgical procedures.

#### MATERIAL

The tests were carried out on seventy-seven subjects. They were placed in two major groups, dependent on whether surgical procedures had or had not been performed.

Group I was composed of subjects who were not operated upon; this group included ten normal subjects and ten patients who had postural or orthostatic hypotension.

Group II was composed of fifty-seven patients who had undergone surgical procedures for interruption of various sympathetic pathways.

Twelve of these fifty-seven patients had peripheral vascular disease. Of these twelve patients, six had been subjected to lumbar sympathectomy; five to cervicothoracic sympathectomy; and one to both cervicothoracic and lumbar sympathectomy. The other surgical procedures were performed on forty-five patients who had essential hypertension. The types of sympathetic section were as follows: (1) bilateral removal of the second, third, and fourth lumbar ganglions and the intervening sympathetic trunk (generally referred to as bilateral lumbar sympathectomy); (2) bilateral removal of the inferior cervical and first and second thoracic ganglions and intervening sympathetic trunk (generally referred to as bilateral cervicothoracic sympathectomy); (3) bilateral resection of the intercostal nerves from

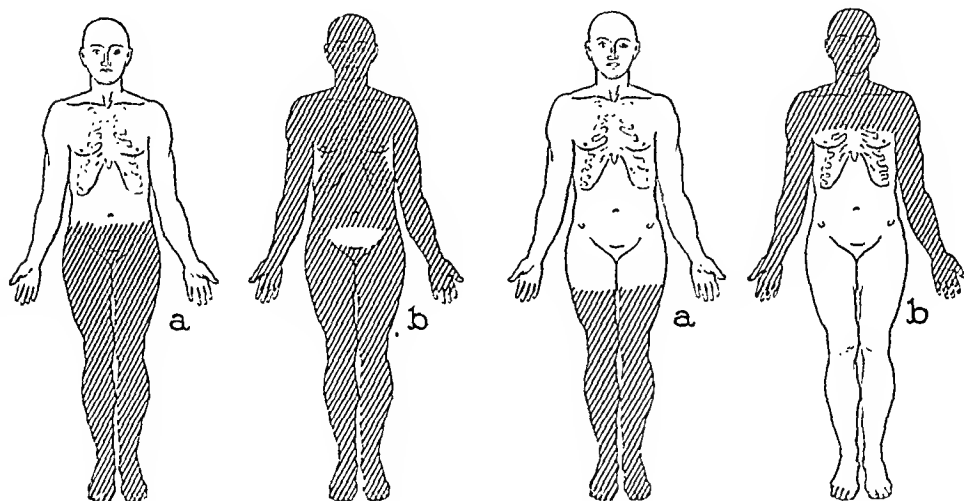


Fig. 1.

Fig. 2.

Fig. 1.—Anhidrosis associated with postural hypotension. In this and in succeeding illustrations, the shaded portions indicate areas of anhidrosis: *a*, usual distribution; *b*, distribution in a severe case.

Fig. 2.—Effects of different operations performed for peripheral vascular disease: *a*, bilateral lumbar sympathectomy; *b*, bilateral cervicothoracic sympathectomy.

the seventh to the eleventh, inclusive; (4) posterior infradiaphragmatic bilateral splanchnic resection with bilateral removal of the first lumbar ganglions; (5) extensive bilateral splanchnic resection, partial resection of the celiac ganglion, partial bilateral resection of the suprarenal glands, and bilateral removal of the first and second lumbar ganglions; (6) bilateral ventral rhizotomy (each of the following inclusive) from the eleventh thoracic to the second lumbar, from the tenth thoracic to the second lumbar, from the ninth thoracic to the second lumbar, from the eighth thoracic to the second lumbar, from the seventh thoracic to the second lumbar, from the sixth thoracic to the twelfth thoracic, from the sixth thoracic to the second lumbar, and from the fifth thoracic to the second lumbar.

## RESULTS

With this method, profuse sweating has been observed over the entire body of normal individuals. In all the illustrations, the shaded portions correspond with the areas of anhidrosis. In the group of patients with postural or orthostatic hypotension, the absence of sweating was found for the most part in an area below the umbilicus, although variations occurred (Fig. 1). The observations following bilateral lumbar sympathectomy and bilateral cervicothoracic sympathectomy have been reported previously by Brown and Adson<sup>6</sup> (Fig. 2). Figures 3 and 4 demonstrate the areas of anhidrosis following various operations performed on patients who had essential hypertension.

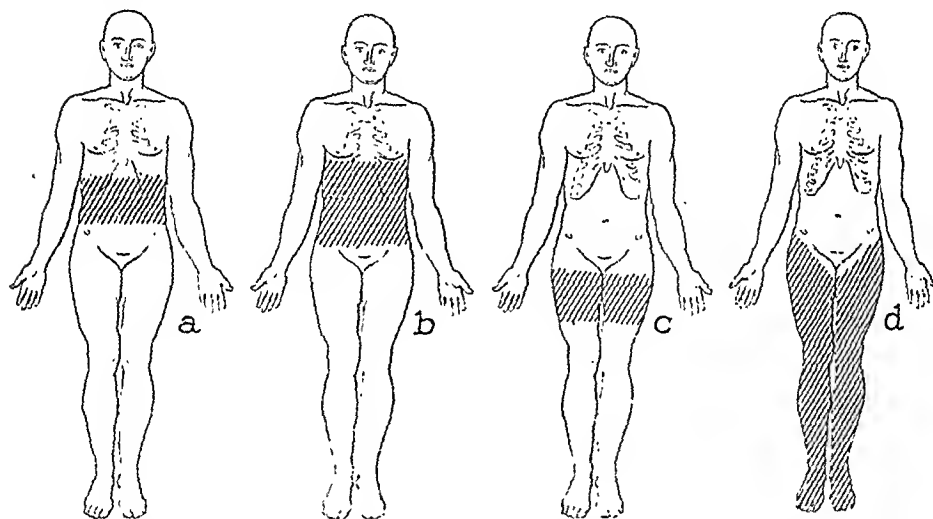


Fig. 3.—Effects of different operations performed for essential hypertension; *a*, bilateral resection of intercostal nerves from the seventh to the eleventh inclusive; *b*, ventral rhizotomy from the sixth thoracic to the twelfth thoracic, inclusive; *c*, posterior bilateral infradiaphragmatic splanchnic resection with bilateral removal of the first lumbar ganglions; *d*, extensive bilateral splanchnic resection, partial resection of the celiac ganglion, partial bilateral resection of suprarenal glands and bilateral removal of the first and second lumbar ganglions.

Figure 3 *d* requires further discussion. It represents twelve patients following extensive bilateral resection of the splanchnic nerves, partial resection of the celiac ganglion, and bilateral partial removal of the suprarenal glands, with bilateral removal of the first and second lumbar ganglions. The patients had, as a consequence, complete anhidrosis from the level of the inguinal sulcus, extending downward and including the lower extremities. In addition, at a subsequent time, to four of these patients  $\frac{1}{16}$  grain (0.01 gm.) of pilocarpine hydrochloride was administered intramuscularly and the areas of anhidrosis noted. These tests were carried out at varying periods following operation. On two patients the tests were made fifteen days after the

final surgical procedure. Under the influence of pilocarpine the first of these patients had slight sweating over the inner aspects of both legs, down to the medial malleoli; with heat, complete anhidrosis was demonstrated in this area. The second patient, except for the feet, did not sweat in the area which had been anhidrotic under the influ-

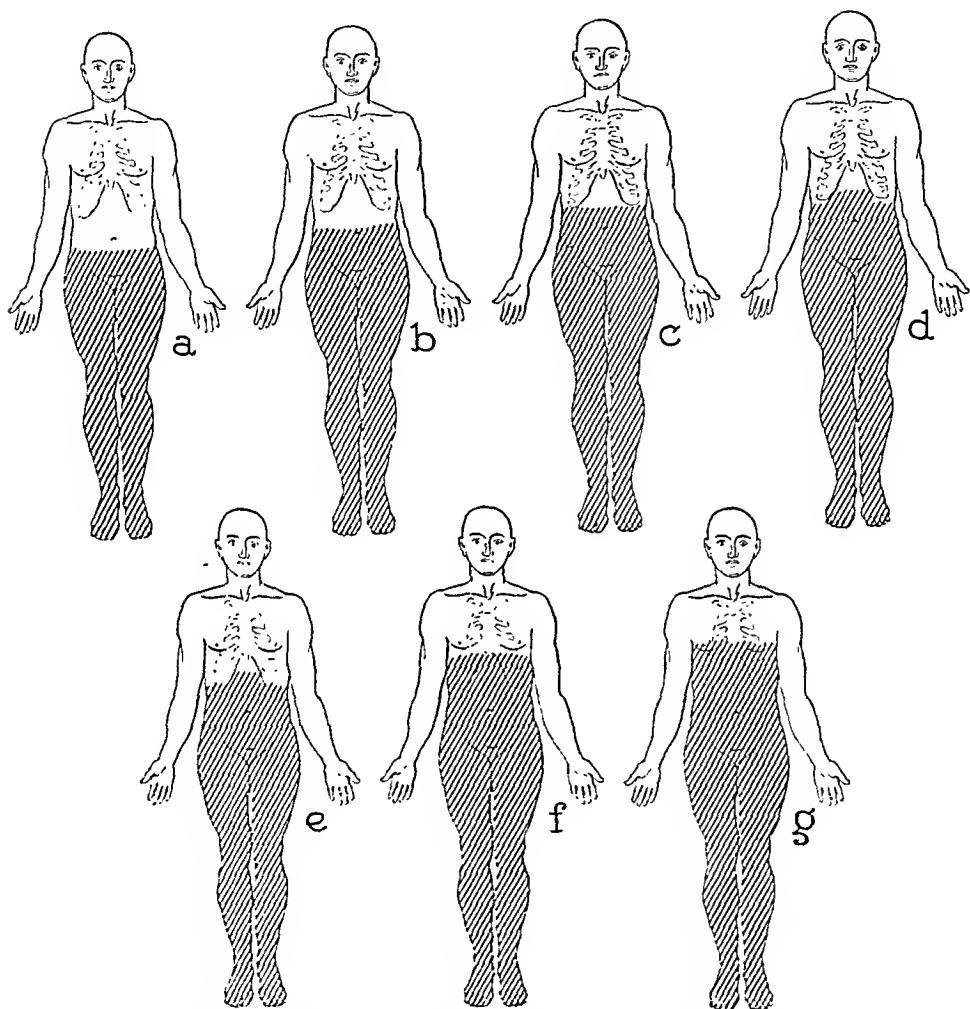


Fig. 4.—Effects of bilateral ventral rhizotomy on patients with essential hypertension: a, eleventh thoracic to second lumbar inclusive; b, tenth thoracic to second lumbar inclusive; c, ninth thoracic to second lumbar inclusive; d, eighth thoracic to second lumbar inclusive; e, seventh thoracic to second lumbar inclusive; f, sixth thoracic to second lumbar inclusive; g, fifth thoracic to second lumbar inclusive.

ence of heat. The test was carried out twenty-seven days after operation on the third patient. In this instance the area of anhidrosis, as demonstrated by heat and by pilocarpine, was the same. Under the influence of pilocarpine, the fourth patient, who was tested with the drug six months after the operation, had only the slightest persistent

sweating over the lateral dorsal aspect of the feet. Otherwise the area of anhidrosis was the same as that demonstrated by heat.

On a fifth patient, on whom cervicothoracic sympathectomy and lumbar sympathectomy had been performed three years previously, complete anhidrosis was demonstrated, by use of heat, over the face, on the chest bilaterally to a level 10 cm. below the clavicle, over the upper extremities and over the lower extremities from the knees downward. Following administration of pilocarpine, however, anhidrosis was present over the entire body, with the exception of the face and axilla, where excessive sweating was noted along with slight sweating on the abdomen.

#### COMMENT

In his early work on cats, Laugley<sup>9</sup> demonstrated a parallel course for the nerve fibers which control vasomotor reactions and sweating. If the vasomotor fibers are completely removed, sweating cannot be demonstrated. In a later work<sup>10</sup> Laugley stated further that, in cats, the area of skin supplied by the gray rami of each ganglion corresponds in the main with the area of skin supplied by the homologous posterior root fibers. This study on man tends to confirm the work of Laugley as to the distribution of the secretory nerve fibers.

Although the diagrams show definite linear levels of anhidrosis, some variations in the line of demarcation of complete anhidrosis were observed. Apparently some overlapping occurred in the segmental distribution of the secretory nerve fibers. Of areas of anhidrosis which included the upper or lower extremities, the driest portions were on the hands and feet respectively. In some instances definite sealing of the feet occurred.

It is generally conceded that pilocarpine has a direct action on the sweat glands. For the most part, tests carried out with pilocarpine within a month following sympathectomy show that sweating can be induced. In these patients, the amount of sweating induced with pilocarpine hydrochloride was diminished before the end of one month. It is of interest to note that under the influence of pilocarpine, the patient who had undergone both cervicothoracic and lumbar sympathectomy three years previous to administration of the drug, excessive sweating occurred over the entire face and neck. This was in contrast to a lack of sweating in this area under the influence of heat. An explanation is found in the recent work of Wilson,<sup>13</sup> who demonstrated a double innervation, both sympathetic and parasympathetic, of the sweat glands of the human face.

The distribution of anhidrosis of patients who have postural or orthostatic hypotension simulated, in many instances, the distribution of anhidrosis following extensive interruption of the sympathetic vasomotor pathways.

# SUMMARY

Following the interruption of various sympathetic pathways, anhidrosis occurred in cutaneous areas that corresponded closely to the segmental level at which the sympathetic nerves were distributed in the spinal nerves. The area of skin supplied by the gray rami of each ganglion corresponds in the main with the area of skin supplied by the homologous posterior root fibers.

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## THE OPERATIVE MANAGEMENT OF FIBROUS CONSTRICTING PERICARDITIS\*

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THE condition of dense fibrosing and calcified pericarditis is by no means as infrequent as is commonly supposed. Its assumed rareness is due to the teaching of clinicians who observe the condition relatively rarely during their lifetime. On the other hand, pathologists very frequently find adhesive pericarditis at autopsy as a secondary finding. These fibrous adhesions are also partly interspersed with considerable amounts of calcium deposit, although they may not have produced any disturbing influences on the heart during life. Hence, it becomes evident that the surgeon sees only the worst cases which are in urgent need of relief.

Two circumstances are responsible for the appearance of grave functional disturbances of the heart: First, the contiguous infiltrative involvement of the mediastinum with a binding of the pericardium to the posterior wall of the sternum (*accretio cordis*); second, the development of concentric shrinking of cicatricial tissue with a constriction of the heart and a throttling of the entrance and exit of the larger vessels (*concretio pericardii retrahens*).

The affections of the pericardium, particularly pericardial effusion, were known to the older physicians, such as Galen, Forestus, and Riolan. However, for a more accurate knowledge of the symptomatology of this pathologic change in the pericardium, we are indebted in recent years to two German teachers who have more accurately studied this condition.

Pick was the first to recognize the symptoms which suggested the diagnosis. Since the whole picture of the disease is deceptively similar to liver cirrhosis, as considerable ascites is also present in this disease, he named it *Pseudolebercirrhose* or pseudohepatic cirrhosis, although he was not able to discern the underlying causes.

On the other hand, Volhard first gave a comprehensive description of the clinical picture which is due to an obstruction of the venous circulation, and which he designated by the term *Einsflusstauung* or inflow-stasis. This stasis is produced by a hindrance to the inflowing blood of the vena cava at the right auricle, causing venous pulsation in

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Received for publication, March 2, 1937.

the neck as well as transudation of fluid in the body cavities (thoracic and abdominal cavities). The liver, being a blood reservoir, in series with the heart also swells and enlarges like a congested organ. Thus, when the disease develops in this manner, it manifests itself by a synchronous retraction and diastolic bulging of the chest wall with each movement of the heart associated with a strikingly small pulse. Very often the calcium-hard cicatrix constricts the heart so firmly that the apex beat can no longer be felt (*"Stille über dem eingemauerten Herzen"*—"Quietness over the encased heart"). Roentgenography, which shows very characteristic changes, greatly facilitates the diagnosis. When the disease is still in the early stage of exudative effusion, the heart shadow appears as an isosceles triangle with the apex above. In the cases which have progressed to cicatricial contraction, one finds a strikingly small heart shadow in which contraction is scarcely discernible. Very frequently the onion-peel arrangement of calcium deposits is observed and occasionally small residual cavities. Kymographic examinations of the heart in different oblique directions clearly reveal the degree of motility still present in systole and diastole, so that from the photograph it is possible to ascertain with a great degree of certainty which parts of the heart are most involved and need release.

Through Volhard's work we have learned to make the diagnosis earlier and to differentiate the disease from mitral stenosis, in which the symptoms are sometimes similar. He wrote: "A functionally similar, or even the same, condition occurs in *concretio pericardii* as in the most severe forms of mitral stenosis. In the latter we likewise find an abnormal output of the left heart, the same small pulse of little amplitude, and an intense inflow stasis with the characteristic elevation of venous pressure, liver enlargement, and preponderant ascites. The increase in venous pressure corresponds to a marked overfilling of the right heart with dilatation of the *conus pulmonalis* and especially the right auricle, which in contrast to the pericardial constriction generally is followed by a permanent irregular pulse. Both the dilatation of the right auricle and the *conus pulmonalis* have a characteristic roentgenographic appearance. The congested cervical veins not only show a diastolic collapse, but also a systolic swelling, because in this stage of mitral stenosis a functional or organic tricuspid insufficiency regularly exists. Indeed, not infrequently we even see a systolic retraction and a swinging movement of the precordial region where the ventricle lies adjacent to the chest wall, which reminds one of the chest wall retraction of mediastino-pericarditis. But instead of quietness over the encased heart, we feel here the mighty heaving action of the right ventricle over the area of cardiac dullness and under the left costal arch and hear the characteristic mitral rhythm and the diastolic murmur over the apex as it strikes the chest wall. In the presence of these a mistake is hardly possible, but it



is theoretically of greatest interest that in different ways this combination of an abnormally small cardiac output with stasis on the venous side of the heart produces the same clinical picture and the predominance of portal stasis over peripheral stasis." Because he was cognizant of these facts, the senior author has never had a mistaken diagnosis in the twenty-two cases he personally operated upon.

The disease begins as a fresh exudative inflammation of the pericardium, which produces marked symptoms, usually subsides in children, and is due either to tuberculosis or metastatic suppuration following rheumatic arthritis.

The early exudative form of the condition has long been treated by aspiration or drainage of the pericardium and has also produced excellent results when the diagnosis is made early.

No one dared operative intervention in the terminal stage, in which the prognosis was grave and life was endangered by cardiac constriction, until 1898, when DeLorme proposed operating for this condition. Apparently his proposal was not put in actual practice—at least there is nothing found in the literature about it.

Brauer inaugurated, in 1902, another type of operation which would relieve the heart of its excessive work ("*Sisyphusarbeit*") of systolic retraction and chest wall movement. He recommended a mobilization of the bony thorax by removing the ribs adhering to the pericardium. This supposedly gave the heart a soft covering instead of a bony one, thus removing from the heart the tremendous additional labor of the chest wall retraction.

This technique, which has been named "*cardiolysis praecardiaca*," unfortunately has very limited indications. It can be employed in only those few cases in which the pericardium is attached only to the posterior aspect of the sternum. In the majority of cases this operation is insufficient, because the principal cause of the functional hindrance is not the attachment to the sternum, but is due to the binding constriction of the heart itself.

For this reason, L. Rehn proposed a further step to DeLorme's technique; i.e., partial resection of the pericardium.

The results obtained by this new operative technique of excision of the pericardium have made it the method of choice. The senior author, in collaboration with the medical clinic under Volhard, first in Halle and later in Frankfurt am Main, has operated upon twenty-two cases.

The prognosis of nonoperative cases in the progressive constricting adhesive pericarditis is absolutely hopeless. With increasing cardiac insufficiency and increasing hydrops and hepatic engorgement, death ensues after months of miserable confining illness.

The cicatricial constriction existing over a long period of time produces generalized injury to the organism which is distinctly manifested

in children with this disease by their marked stunting in bodily development, so that they very rarely reach puberty when they are not operated upon.

Remarks of young patients who have undergone operation, such as "I am stronger and now take part in athletics" or "I am feeling fine

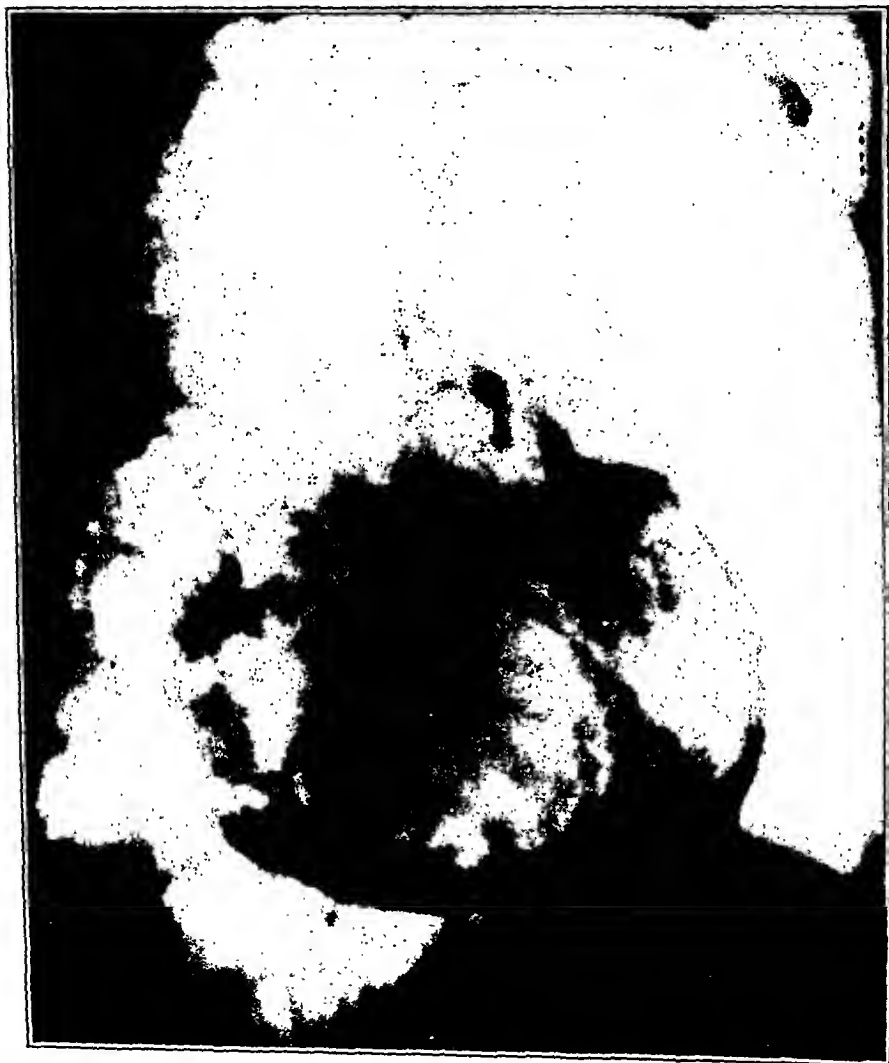


Fig. 1.—X-ray pictures of the heart which is surrounded by extensive calcified scarring.

and am very happy about it," should be an indication for operation, even to a hesitating surgeon.

The operative management begins with a very intensive preoperative medical treatment. The burden on the heart must be lightened by relieving the marked hydrops. The administration of a sodium chloride-

free diet and the utilization of diuretics aid in diminishing edema. In order to completely remove the excess fluid, it is often necessary to aspirate the pleural and peritoneal transudates. If following these measures the heart functions better, its activity can be strengthened and its beating regulated by sufficiently large doses of strophanthin.

The difficulties of operative intervention will be greatly diminished if local analgesia is used whenever possible. Numerous investigations have shown that the precordium and heart musculature are completely insensitive, so that one can depend solely upon the technique of a good local analgesia.

For exigency, the positive pressure apparatus should always be available for use during the entire operation, so that in case a large tear of the pleura occurs, the defect can be sutured under forced respiration. In excision of the pericardium the anterior margin of the left pleural fold (*Complentärraum*) is the most likely place to tear. Very often here an extremely delicate pleura borders upon a dense calcified pericardium, so that a complete backward mobilization of the pleura cannot always be done.

Before resection of a portion of the pericardium was done, the question arose whether this would be possible without damage to cardiac function. Numerous physiologic experiments, especially the fact that no disturbance ever appeared following operation, and the magnificent results of operation have shown that no damage whatever occurs to the heart.

As a result of the long-existing fibrosing constriction of the heart musculature, it often unfortunately undergoes an inactivity atrophy, so that its strength and function are considerably impaired.

Because of the anatomic position of the heart, in that the right ventricle occupies the most anterior position, the surgeon is likely first to free this chamber, which has a weaker musculature. If the weak musculature of the right ventricle is suddenly deprived of its callous support by decortication, while the left ventricle remains encased in scar, it can no longer resist this additional burden and dilates or even ruptures. Thus, this technical error may result in acute dilatation of the heart associated with tricuspid insufficiency. A single unfortunate experience of such an overdilatation which led to a fatal termination on the table demonstrated this great danger to Schmieden and he suggested appropriate measures to be used in preventing it. Therefore, the operative technique is based upon the following fundamental principles: (1) liberation of the left ventricle first, in order that it can receive and immediately deliver to the systemic circulation the increased output of the right ventricle following its subsequent decortication and thus avoiding the right-sided venous congestion that would otherwise occur; (2) freeing of the right ventricle, which then usually dilates more effec-

ciously and beats stronger. The final freeing of the right heart should be done in a systematic successive manner. Owing to the thin wall of the auricles, these should not be freed.

Whereas previously there was considerable discussion as to the extent of the decortication, at the present time the important question is a consideration of what parts of the thickened pericardium should be allowed to remain as support to the weakened heart musculature. Because of the above described danger of an acute trienspid insufficiency and also in order to avoid the development of deficiency of the auriculoventricular valves, thus leading to the immediate occurrence of an inflow venous congestion, the decortication should never be performed beyond the coronary sulcus.

With a cognizance of these fundamental facts, the operative technique of Schmieden was evolved in the following manner: "The type of skin incision may vary considerably and is, in the main, rather unessential. The third to the fifth costal cartilages inclusive, with the adjacent portions of the ribs and a large portion of the sternum, are resected. I have an impression that a large window in the chest is more conducive to a lasting recovery and further favors later mobility of the heart in its new bed. Thus, the *pericardiectomy* begins with the *cardiolysis praecardiaca*.

"Following this I recommend the attempt to proceed toward the pericardium between the two unopened pleural layers. The adjacent costal and mediastinal pleurae are usually thickened enough so that their tearing can be very well avoided. However, the availability of the positive pressure apparatus is necessary, because if an accidental opening of the pleura should occur it can be sutured immediately without any untoward incident. Transpleural approach may occasionally permit the pericardium to be reached more quickly, but because of the phrenic nerve it is not the most suitable position and may result in postoperative complications. Considerable difficulties may be encountered in effecting hemostasis in this chronically inflamed tissue, and in spite of all efforts it may often be incomplete. Therefore, two or three small drainage tubes are employed in closing the wound, which heals by primary union. After the removal of the tubes there may be slight bleeding or an abundant serous discharge which escapes between the sutures. The adequate removal of this fluid undoubtedly contributes toward healing without recurrence.

"The question of how liberation of the heart should be done after mobilizing the pleura may be answered best by a comparison. It is peeled not like an apple, but like an orange. The secret is to get into the correct line of cleavage, and after pulling off the coarse mantle, to continue excision of the separated strips of pericardial callus until one can see the muscle fibers of the heart everywhere, which become visible

as each successive piece of scar tissue is extirpated. Also in this regard the procedure is similar to the peeling of an orange, because one must afterward clean off scar tissue at different sites."

In order to immobilize the free-lying border of the anterior pleural fold, for the past few years the senior author has attached it to the left

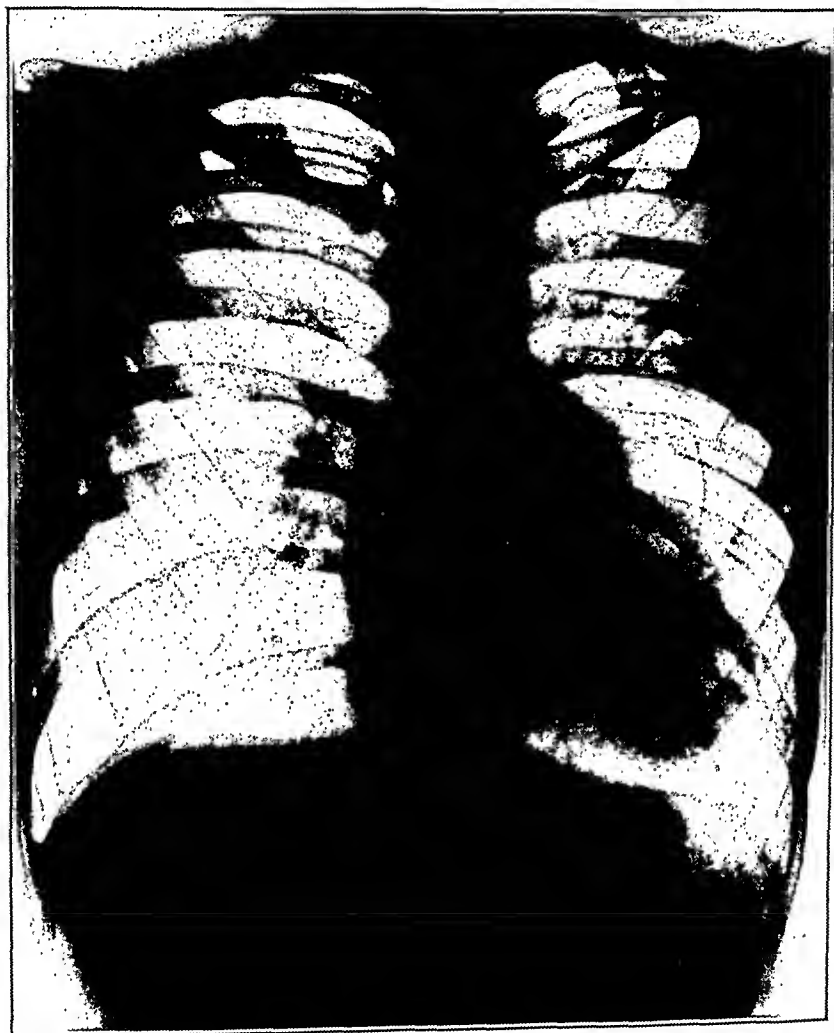


Fig. 2.—X-ray pictures of a case of pericarditis four years after operative liberation. The hernia-like protrusion of the left ventricle is very distinct.

margin of the thoracic window and thus also protected it during operation. This technique he terms "*Exopericardiopexie*."

After the completed operation, the pectoralis muscle is excised in order not to form an undesirable adhesion to the heart, and the skin flap with the adhering subcutaneous fat is replaced and sutured.

The arrest of hemorrhage is usually not completely effected so that for a short period of time several rubber drains are placed in the wound. This drainage may perhaps account for disturbances which occur in the postoperative course, because the atmospheric air is now in contact with the free-beating heart. On these grounds, avoidance of drainage has been advocated in the Anglo-American literature in order to prevent the atmospheric variations in pressure.

Special attention must be given the apex of the heart which is usually firmly fixed and considerable difficulty is encountered in the attempts to liberate it. If decortication of the apex of the heart, which is bound down to the diaphragm, should not be successful, normal systolic contraction is impossible, because during inspiratory depression of the left dome of the diaphragm the heart is elongated and during systole becomes lancet shaped. In order to remedy this undesirable condition left-sided phrenicotomy is generally recommended, since this results in sufficient relief.

The entire operation can usually be performed through an anterior flap incision described by the senior author. In his twenty-two cases, he was obliged only once to do a second-stage operation in order to free a larger portion of the left ventricle. This second intervention was achieved transpleurally through an intercostal incision. This method of approach should be reserved for cases in which one particularly wants to free only the left ventricle. It has advantages and disadvantages. The results of operative management with a consideration of all details follow:

27.3 per cent (6 cases)	Perfect healing with restoration of full ability to work
27.3 per cent (6 cases)	Very marked improvement and preservation of life after long observation
4.5 per cent (1 case)	Death at operation of acute dilatation of the right ventricle
31.9 per cent (7 cases)	Death during postoperative period
9.0 per cent (2 cases)	Death after transitory improvement

The last two groups of death which unfortunately occurred during the postoperative period or after a transitory improvement may seem discouraging, since this forms 40 per cent of the whole material. The high postoperative mortality is due to the dangers caused by the sudden appearance of insufficiency of the cardiac musculature which has been freed from its constriction and thus deprived of its support. In considering these results of operation, it must be remembered that the great majority of the cases were far advanced and had an extremely bad prognosis.

The best criterion of the operative success and of the state of the heart is the venous pressure. Also, after a successful operation for a

period of time the heart needs the help of strophanthin. As regards the diet, the patient should be restricted in several respects: Fluids are limited and a diet poor in sodium chloride is prescribed. For this reason, the close cooperation of an internist before and after the operation is very necessary.

The death of most of the patients, even after a transitory improvement, was due to their primary disease, which in almost all the cases was tuberculosis of the lungs or the bronchial lymph nodes. While writing this paper, there is a young female patient in preparation for operation. Thus far, the clinical course of her disease and the x-ray pictures indicate a relatively good prognosis. It is very probable that in this case, which is the first to be admitted to the clinic in such good general condition, it will not be necessary to perform extensive excision of the pericardium, but probably the removal of only a small strip of constricting scar will suffice. Greater interest should be aroused in the early symptomatology of dense, binding, fibrosing pericarditis, so that patients are brought to the surgeon while they are still in good general condition and have an efficient cardiac action. Only under these circumstances will it be possible to do away with extensive resection of the pericardium and to be able to do in the future only the simple separation of the armor plate. Under these circumstances we shall be able to save many a life which has been considered as lost.

# HIGH FREQUENCY TRANSMISSION OF STIMULATING IMPULSES

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THE importance of electrical stimulation of nervous tissue in physiologic research needs no comment. In acute experiments it is not difficult to stimulate directly the exposed nerve in the anesthetized animal, and much of our knowledge of neurophysiology has been obtained in this fashion. Nevertheless, the need for a satisfactory method for obtaining prolonged stimulation in the intact, unanesthetized animal long has been felt.

The permanent implantation of electrodes in the subject, with wire leads carried to the surface of the body, where they might be connected to the source of stimulating current after the recovery of the animal from operation, was pioneered by Hess.<sup>1</sup> This method has a limited sphere of usefulness because of the impossibility of maintaining the point of exit of the wires in a sterile condition over long periods and the restriction of free motion of the subject under stimulation.

In order to eliminate the necessity of connecting the electrodes and the source of stimulating current, the idea was conceived of substituting electromagnetic coupling. Chaffee and Light<sup>2</sup> made use of a periodically charged condenser of large capacity which discharged a very considerable current through a coil thirty-six inches in diameter. This discharge produced an intense electromagnetic field, so that a small coil implanted in the subject received an induced current which was carried by wire leads to the structure to be stimulated. The subject was confined in a twenty-inch cubical cage suspended in the center of the primary coils. It was found necessary to have three primary coils, in three planes mutually perpendicular to each other so that effective coupling could be maintained regardless of the position of the secondary coil. The three coils had to be energized in sequence, and for this purpose an elaborate vacuum tube switching circuit had to be devised to handle the heavy current.

At about the same time, and independently, Fender<sup>3</sup> devised an apparatus in which the primary coils were energized by 60 cycle

Received for publication, April 12, 1937.



alternating current from lighting mains. Six coils were employed, two in each of the three planes, giving a very uniform field intensity in the central cage in which the subject was placed. The implanted coil was of 6,000 turns of very fine wire and was somewhat smaller

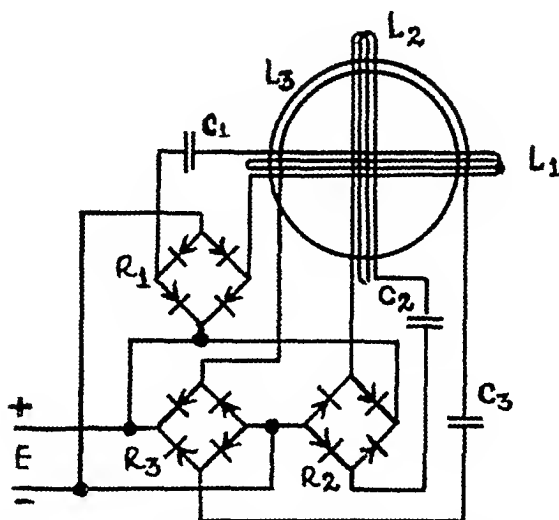


Fig. 1.—Implanted unit.  $R$ , copper oxide rectifiers;  $C$ , .00025 mfd mica condensers;  $L_1$  and  $L_2$ , coils of 145 turns No. 30 enameled wire wound perpendicularly over  $L_2$ , a similar coil of 110 turns;  $E$ , electrodes. Outside diameter  $1\frac{1}{2}$  inches.

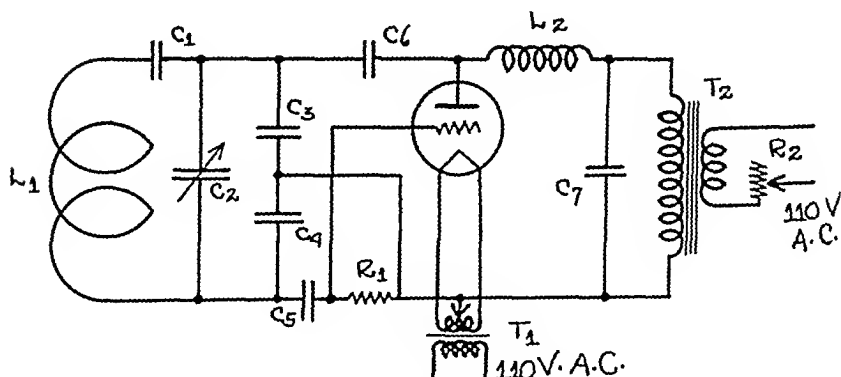


Fig. 2.—High frequency supply circuit.  $L_1$  consists of 6 turns of No. 14 wire around an enclosure 5 feet square;  $L_2$ , choke coil of 1,000 turns No. 24 enameled wire on a 2-inch form;  $C_1$ , mica condenser .002 mfd;  $C_2$ , variable condenser .00025 mfd;  $C_3$ , mica condenser .002 mfd;  $C_4$ , mica condenser .01 mfd;  $C_5$ , mica condenser .002 mfd;  $C_6$ , mica condenser .00025 mfd;  $C_7$ , mica condenser .004 mfd;  $T_1$ , filament transformer;  $T_2$ , transformer with secondary voltage 2,500 v.;  $R_1$ , resistor 5,000 ohms;  $R_2$ , rheostat 120 ohms for control of plate voltage. Vacuum tube oscillator is RCA 806.

than that of Chaffee and Light. The paired coils were energized in sequence, a mechanical switching arrangement being employed.

Both of these methods produced good results but had certain limitations. The subject had to be closely confined. If the cage in which

the animal was placed was increased in size over the minimum requirements for small subjects, really tremendous currents were necessary; this, in turn, necessitated elaborate and expensive switching apparatus to energize, successively, the coils in the three primary planes. In addition, the necessity of exciting the coils in sequence meant that when the implanted coil was in any of the three planes it received induced current only a third of the time. Moreover, while Chaffee and Light were able to change the frequency of the stimulating impulses, the wave form depended upon the condenser discharge.

We have modified the previous methods in two important respects: first, a current at high frequency is used to energize the primary coil, thus taking advantage of the greatly increased induction incidental to the increased rate-of-change of flux within the field and the resulting ability to use much smaller currents. Current at the frequency now used, 450 kilocycles a second, does not, of course, stimulate nervous tissue. But we have found it possible to rectify the current induced in the secondary coil by means of a very small copper oxide rectifying unit such as is used in instruments measuring alternating current. The current delivered to the stimulating electrodes depends for its characteristics, both as to frequency and wave form, on the modulation of the source of high frequency current energizing the primary coil.

Second, instead of using three primary coils, with the attendant difficulties of energizing them in sequence, it is now possible to construct a single unit for implantation consisting of three coils mutually perpendicular to each other; each with its individual rectifier, but all connected to the two stimulating electrodes. The entire unit has a diameter of  $1\frac{1}{2}$  inches and a maximum thickness of  $\frac{5}{16}$  inch. By this expedient the output at the electrodes is kept approximately constant regardless of the position of the animal.

The apparatus in operation at present consists of a simple vacuum tube oscillator, modulated at 60 cycles by the ordinary commercial current, which delivers approximately 150 watts at 450 kilocycles to a single coil of six turns of No. 14 insulated copper wire placed in the walls of a five-foot room. One or several animals may occupy this room, during stimulation, in relative freedom.

The strength of the field within the room is relatively constant, an output of 4.0 milliamperes being obtained from the implanted unit through an external resistance of 2,000 ohms, in the center of the room. A thorough trial, with a number of implantations with electrodes in contact with the cerebral cortex, skeletal and sympathetic pathways has shown this current to be more than adequate for stimulation.

The secondary unit is so adjusted that its resonant frequency is equal to that of the primary circuit. Since the frequency of the primary current may be varied by tuning this circuit, it is possible to implant two or more secondary units and to energize whichever is desired by tuning the primary to that particular frequency.

In summary, the apparatus here described makes it possible to stimulate nervous tissue in an animal that is free to lead a normal laboratory existence, for an extended period, with any wave form or frequency desired. More than one coil may be implanted and each may be stimulated at will. All materials required are readily obtainable and relatively inexpensive.

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## SOME ASPECTS OF ECHINOCOCCUS DISEASE

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### LIFE HISTORY

THIS disease is due to the development in the human subject of the cystic or larval stage of the *Echinococcus granulosus* (Batsch), a small cestode whose natural habitat is the small intestine of the dog. The adult worm measures up to 6 mm. in length and possesses three or four segments, the terminal one of which carries from 500 to 800 ova in various stages of development. These worms may be present in thousands in an infested dog, and the intact or disintegrated mature segments are shed in the feces.

The ova, approximately 35  $\mu$  in length, are, like those of the other cestodes, surrounded by a chitinous envelope and are extremely resistant to exposure. Under favorable etiologic conditions, they may be ingested by the correct intermediate host in which the cystic stage of development takes place.

### ETIOLOGY AND PROPHYLAXIS

Although the worm has been occasionally found in other canines, owing to his cosmopolitan distribution and close association with man, the dog is practically the only source of infestation. This animal is infested by eating fertile hydatid cysts in the viscera of animals which can act as intermediate hosts, nearly always the domesticated sheep, ox, or pig. It is found that the incidence of the disease in man follows accurately that in the domestic animals of the country and that the sheep is the most important intermediate host. For this reason the disease is common in Iceland, Australasia, Algeria, and South America. It is rare in North America, although many sheep are pastured there. It would seem, however, that if a close association persists between men, dogs, and sheep, the disease will gradually increase in frequency there.

Man acts only as an immediate host, occupying the same biologic position as the sheep; but owing to the fact that dogs do not have access to human viscera, such infestations must be considered as a dead end as regards completion of the parasitic life cycle. In the past, great importance has been attached to the contamination of water or fresh vegetables as an etiologic factor, but there is no doubt that con-

Received for publication, May 26, 1937.

tamination of the hands by direct contact, i.e., by handling and caressing dogs, is far more important. This explains the relatively high incidence in various occupations, the frequency of more than one case in a family, the almost equal incidence in the two sexes, and the frequency of infestation during childhood, the age of promiscuity with the dog and unhygienic behavior generally. One must realize that the majority of infestations occur in childhood, although owing to the slow growth of the cyst, the disease often does not manifest itself until adult life. It may be taken as a general rule that an hydatid cyst in man is nearly as old as the patient harboring it.

Owing to the existence of two distinct evolutionary cycles in the life of the parasite, prophylactic measures are easy and should be applied in two ways: first, by preventing infestation of the dog by controlling his access to infested viscera; and second, by educating people concerning the danger of contact with possibly infested dogs.

#### DEVELOPMENT OF THE CYST

Following ingestion by the intermediate host, the ovum hatches in the upper alimentary canal, liberating an active six-hooked embryo, which bores through the wall of the gut and, entering a radicle of the portal vein, is carried to the liver where in the majority of cases it comes to rest and where its typical further development is seen. At first there is an active cellular reaction on the part of the host defences—mononuclear and eosinophil cells surrounding the parasite which may then undergo disintegration and phagocytosis. In favorable cases, however, it grows rapidly and with the same dramatic changes that characterize all embryonic growth, so that at the end of three weeks it shows vacuolation with the elaboration of specific fluid and a protective outer wall.

As the parasite grows, the cellular reaction to the host dies down, probably coincident with the development of the semipermeable, laminated, parasitic cuticle, and so the cessation of leakage of specific protein. The leucocytes which surround the follicle become gradually converted into fibroblasts, and toleration of the parasite by the host is established.

The fully developed cyst consists of a double layered parasitic wall composed of an outer laminated membrane and an inner germinal layer surrounding specific hydatid fluid.

The laminated layer is composed of laminae of hyalin which are laid down from within out by the nucleated germinal membrane which lines its inner aspect. It is very elastic, tends to turn inside out when torn, and serves to act as a support for the cyst, and, owing to its selective permeability, prevents the entry of noxious substance. The specific hydatid fluid is also elaborated by the germinal mem-

brane and normally is clear, containing little or no protein, but up to 0.2 per cent sodium chloride. It acts as a buffer and nutritive medium for the developing scolices.

The scolices or future worm heads are found only in mature cysts and are a sign of completed biologic development. They are produced inside brood capsules from the germinal membrane and may be present in thousands in a single cyst, a fact which gives some idea of the prodigality of nature where reproduction is concerned. They are just visible to the naked eye (measuring up to  $160\ \mu$  in the rest-

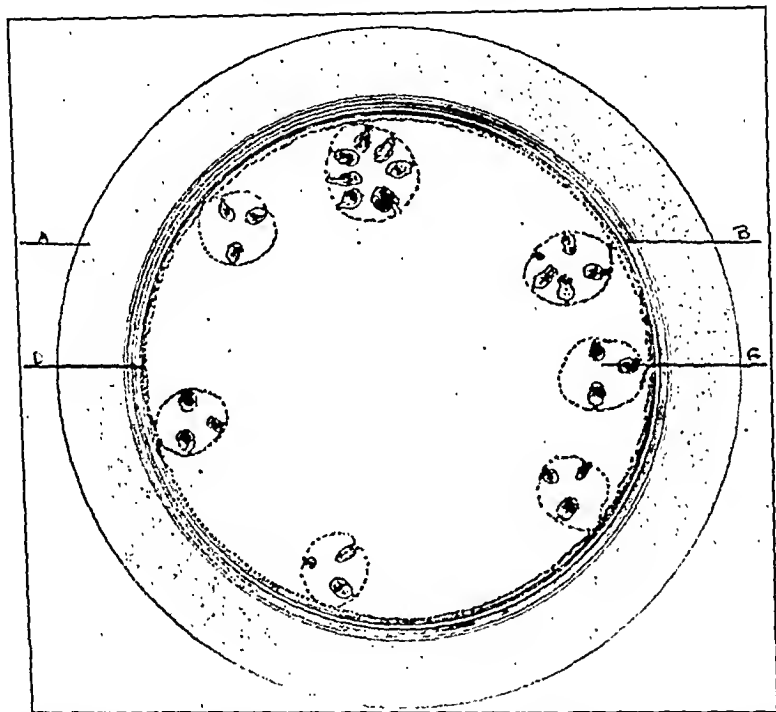


Fig. 1.—Schematic representation of a typical unilocular hydatid cyst, showing A, adventitia; B, laminated membrane; C, germinal membrane; and D, brood capsules containing scolices.

ing state) and are seen in all stages of development—from the undifferentiated cellular bud to the fully developed scolex with suckers, hooklets, and contractile tissue. When swallowed by the dog, they become active and rapidly develop into adult worms, and so the life cycle is completed.

Frequently in man and occasionally in other animals, daughter cyst formation is noticed. This in its typical endogenous form consists of the development within the confines of the original mother cyst of numerous replicas of the primary cyst. There has been much controversy as to the reason for this development, but probably it should be regarded as due to some interference with the integrity of the

original cyst; i.e., that it is a protective phenomenon, the germinal elements being stimulated by adverse conditions to elaborate a second protective cuticle in order that the development of the reproductive elements may go on.

#### CLINICOPATHOLOGIC CONSIDERATIONS

In man the majority of primary cysts are found in the liver, this organ acting, as it were, as a filter; but sometimes the parasite passes the hepatic capillaries and enters the pulmonary circulation, the lungs being the next most common site. The parasites may even pass the pulmonary capillaries and make their way to any part of the body, and the lessening proportionate incidence, as the periphery of the body is reached, indicates that distribution by the blood stream is the only rational explanation. The following table gives the commonly accepted figures for primary cysts:

#### DISTRIBUTION OF PRIMARY HYDATID CYSTS

Liver	76.6
Lung	9.4
Muscular and subcutaneous tissue	5.2
Kidney	2.3
Spleen	2.1
Bones	0.9
Orbit	0.7
Brain	0.6
Other sites	2.2

Multiple infestations are more common in the human subject than is usually realized, more than one cyst being present in at least 60 per cent of cases.

#### UNCOMPLICATED CYSTS

From both the clinical and the pathologic point of view, cysts may be divided into complicated and uncomplicated cysts. It is important to realize such is the latency of many cysts that it is often only the onset of some complication which produces the first symptoms and so draws attention to the lesion.

Uncomplicated cysts comprise all the simple univesicular cysts and some multivesicular (containing daughter cysts) cysts, which have remained noninfected and intact. The simple cysts are found typically in children and young adults; the multivesicular, in older patients; and all are surprisingly well tolerated. This is due to their extremely slow rate of growth, which enables compensatory changes to occur, and to the fact that the cyst is shut off from the body fluids of the host by a relatively impermeable fibrous and laminated layer.

#### UNCOMPLICATED HEPATIC CYSTS

The right lobe is involved in 80 per cent of the cases and the cysts project on the abdominal aspect in 70 per cent of the cases. Clini-

cally, the outstanding feature is the latency and many cases have been recorded in which enormous cysts have existed for years without causing symptoms. This is particularly the case with cysts of the upper quadrants, where the protected site enables them to grow quietly, very often until middle age, without causing obvious symptoms.

Pain in these cases is very rare, and when it occurs it is nearly always indicative of the onset of some complication such as leakage with or without infection. Gastric disturbances which appear to be due to pressure effects are common in long-standing cysts, but they are as a rule vague and not serious. Other pressure effects are sometimes seen and depend on the site and the size of the cyst; it is surprising what very large cysts may be tolerated. In cases in which the cyst exerts pressure on the diaphragm, some dyspnea may be produced. Examination may reveal a rounded, nontender, tense, cystic swelling continuous with the liver dullness. The swelling moves with respiration, but has to be distinguished from other lesions of the right hypochondrium. It is important to realize that cysts of the left lobe of the liver tend to descend anterior to the stomach, while those of the right lobe tend to be on a more posterior plane. In centrally or superiorly placed cysts, the only finding may be hepatomegaly with varying degrees of upward extension of hepatic dullness. In these cases which tend to appear in older subjects, the elevation of the diaphragm may be extreme and the simulation of intrathoracic conditions very accurate.

Radiography is of value in the diagnosis of these cysts, because it may show diaphragmatic elevation or distortion or in older cysts some calcareous changes in the adventitia.

#### UNCOMPLICATED PULMONARY CYSTS

Owing to the vascularity and loose nature of the tissue, pulmonary cysts grow evenly and fairly rapidly, producing as a rule a relatively thin adventitia covering. The typical cyst is univesicular, containing scolices but no daughter cysts, and it may occupy a parabronchial or peripheral situation, sometimes almost filling the chest cavity. Even in the case of large cysts, pleural adhesions are rare. The bases of the lungs are involved more than the upper parts and the right side more than the left in the proportion of 60 to 40.

Clinically, these cysts are also remarkably latent, and it is doubtful whether more than 25 per cent are discovered before the onset of some complication. Sometimes the first indication of their presence is delay in resolution of some respiratory infection like bronchitis or pneumonia. A dry cough is classical and common and seems to be independent of the size or site of the cyst. Hemoptysis is the most common symptom, being present at some time or other in 60 per cent of cases and varying greatly in degree. There is, as a rule, no ex-



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Small cysts in special situations such as the orbit, cranial cavity, or spinal canal may produce grave symptoms relatively early.

#### COMPLICATED CYSTS

Ultimately, however, in all the above, no matter what the situation, complications occur, their frequency increasing as age advances and the cyst increases in size. They are relatively rare in young subjects, manifesting themselves usually between the ages of twenty-five and forty years of age. Practically all complications depend on an escape of fluid from the cyst, this varying from a slight leak, often masked by other symptoms, to a frank rupture.

#### RUPTURE OF THE CYST

As the cyst enlarges, it may encroach on a natural channel, a hollow viscus or serous cavity, one area of the laminated membrane thus becoming relatively unsupported. As a result it gives way spontaneously, even during sleep, following muscular movement, coughing, straining, or more commonly following direct trauma such as a blow, a fall, a crush, or a perforating injury. Owing to its peculiar grain, the tear in the laminated membrane rapidly enlarges and allows the escape of the contained fluid and hydatid elements. Such rupture takes place commonly into the subcutaneous or muscular tissues, the bile ducts, bronchi, alimentary canal, or urinary tract; into serous cavities, such as the peritoneum, pleura, or pericardium; or very rarely into the chambers of the heart or large veins.

Each of these has its own characteristics, and as some of them may be combined in the individual case, a complete discussion is outside the scope of this article. The sequelae may be grouped together in the following way:

1. *General*: applicable to all types: (a) immediate, hydatid anaphylaxis; (b) delayed, secondary echinococcosis.

2. *Special*: applicable to cases of rupture into a natural channel: (a) immediate, mechanical effects; (b) delayed, death of the cyst with or without suppuration.

#### HYDATID ANAPHYLAXIS

Many clinicians have noted the appearance of peculiar toxic manifestations following rupture or puncture of hydatid cysts. Although these are usually cutaneous, many other symptoms may occur, and there is no doubt that these are mainly anaphylactic, due to the sudden absorption of specific protein in a sensitized patient. Clinically, whenever vague symptoms arise during the course of hydatid disease, the question of whether or not they are anaphylactic in nature should always be considered. The following table gives some idea of their protean nature and illustrates some of the risks of indiscriminate puncture of an hydatid cyst.

peccoration and no pain and little if any dyspnea, even in large cysts.

On physical examination, palpation rarely reveals any cardiac displacement, even in large cysts. There will be diminished vocal fremitus over any area impinging on the chest wall, and further examination may reveal the signs of local tumor with appropriate signs on auscultation.

#### THE DIAGNOSIS

Phthisis is the arch simulator, but the basal situation of the lesion and the lack of confirmatory signs of tuberculosis usually lead to its



Fig. 2.—Radiograph of unruptured, right-sided pulmonary cyst in a patient aged twenty-four years. Oblique view.

exclusion. Radiography, owing to the fact that the saline content of the cyst is relatively radiopaque, has revolutionized the diagnosis of these cases, and great accuracy both as regards the size and localization of the cyst is now possible (Fig. 2). It is, of course, necessary to exclude all other forms of intrathoracic tumor, while the presence of a pleural effusion may at times introduce difficulties in the region of the diaphragm.

#### OTHER SIMPLE CYSTS

Uncomplicated cysts may involve practically any organ or any tissue, and as a result bizarre and protean manifestations may be produced.

Small cysts in special situations such as the orbit, cranial cavity, or spinal canal may produce grave symptoms relatively early.

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## ANAPHYLACTIC SYMPTOMS IN TWENTY CASES OF HYDATID DISEASE

SITE OF CYST	COMPLICATIONS	CA-SONI TEST	DYSP-NEA	COUGH	CYANOSIS	CARDIAC	AGITATION	PYREXIA	URTICARIA	PRURITUS	VOMITING	DELI-RIUM	PUL-MONARY EDEMA	DI-LATED PULS	DEATH	REMARKS
Liver	Bile duct rupture	?	+	+	+	+	+	+ D*	+ D	+	+	-	-	+	-	Three attacks
Heart	Rupture	?	+	+	+	+	-	-	-	-	-	+	+	+	+	
Lung	Cardiac rupture	?	+	+	+	+	-	+	+	+	-	-	+	+	+	
Spine	Rupture of daughter cysts	+	-	+	-	+	-	-	-	+	-	-	-	-	-	Repeated postoperative
Liver	Bile duct rupture	+	+	+	+	+	+	+	-	+	+	-	-	-	-	Many previous operations
Liver	Bronchial rupture	+	+	-	-	-	-	-	+	+	-	-	-	-	-	In convalescence
Liver	Casoni test	+	+	+	+	+	+	+	-	+	+	+	+	+	+	Very small dose
Lung	Rupture into pulmonary artery	?	+	+	+	+	+	-	-	-	-	-	-	-	-	
Liver	Peritoneal rupture	?	+	+	-	+	+	-	+ D	-	-	-	-	+	-	
Liver	Pleural rupture	?	+	-	-	+	+	+ D	-	+	+	-	-	-	-	Postoperative
Liver	Biliary rupture	?	+	-	-	+	+	+	+ D	+	+	-	+	-	-	Postoperative
Liver	Pleural rupture	?	+	+	+	-	+	+	+	+	-	-	+	-	-	
Liver	Bile duct rupture	?	+	+	+	+	+	+ D	+	+	+	-	+	-	-	Many previous operations
Lung	Pneumothorax	?	+	+	+	+	+	+	+	+	+	-	+	-	-	
Omentum	Rupture	?	+	-	+	+	+	+	+	-	+	-	+	-	-	
Pelvis	Leak	?	+	+	-	+	+	-	+ D	+	+	-	-	-	-	After eight days
Omentum	Leak	?	+	+	-	+	+	+ D	+ D	+	+	-	-	-	-	Postoperative symptoms
Liver	Postoperative	+	+	+	-	+	+	+ D	+	+	+	-	-	-	-	
Liver	Peritoneal rupture	+	-	+	-	+	+	+	-	+	-	+	-	-	-	
Liver	Puncture	?	+	-	+	+	+	-	+ i.m.	+	+	-	-	-	-	

\*D = delayed reaction; i.e., after 12 hours.

## SECONDARY ECHINOCOCCOSIS

Rupture of an hydatid cyst or puncture by a trocar with evacuation of the specific fluid does not necessarily cause the death of the parasite; this probably rarely occurs unless infection takes place. The parasitic elements have such powers of persistence that if aseptic conditions pertain they can survive and ultimately develop into new cysts, often at a distance from the original, this phenomenon being described as secondary echinococcosis.

At first, clinicians and pathologists regarded all cases of multiple cysts as due to multiple primary infestations, but they gradually recognized that many were due to secondary cyst formation from implanted scolices. Even as late as 1900, however, the view that such highly differentiated structures as scolices could, as it were, revert in their life cycle, ranked with many authorities as a biologic heresy, as it seemed contrary to all the laws of the development of the cestodes laid down by Van Beneden. Much experimental work and many correlated clinical and pathologic investigations, however, have proved conclusively that such a retrogressive metamorphosis is not only possible, but relatively common and of great clinical importance. Recognition of this has led to great advances in our understanding of the pathology of hydatid disease.

## CLINICAL TYPES

*Localized Secondary Echinococcosis.*—A common example of this is rupture of a subcutaneous or muscular cyst when congeries of small secondary cysts, often called seed hydatids, are commonly found. Of a similar nature are those cases of postoperative or posttraumatic recurrence in the site of the original cyst; one type of local daughter cyst formation.

## SECONDARY CYSTS OF THE PERITONEUM AND PELVIS

These are very common and are due to leakage of scolices from a primary cyst of the liver or, more rarely, of the spleen, kidney, or omentum.

When the cyst ruptures, hydatid scolices are shed into the peritoneal cavity with the production of some anaphylactic shock. The scolices may be shed in thousands and are carried by the rush of fluid, by gravity, or by intestinal movement, as a rule to the lower quadrants. They soon become surrounded by lymph and eosinophil leucocytes and are rapidly fixed in a secondary site. Doubtless many of them are overwhelmed and undergo fibrosis; sometimes the peritoneal reaction around these disintegrating scolices is so extensive that a pseudotuberculous appearance is produced. Many, however, survive, become surrounded by a new adventitia, undergo vesiculation, and

develop into secondary cysts. As in the case of any other foreign body, the peritoneum gradually spreads over until the secondary cyst gives the appearance of having developed in an extraperitoneal situation. It was nonrecognition of this simple process that led many of the older pathologists to believe that these cysts were multiple cysts developed from numbers of hexacanth embryos.

These secondary cysts are of slow growth, there being a latent period of from five to twelve years during which growth takes place until they in their turn produce symptoms. Owing to the usual rapid recovery from the initial rupture, it is often misinterpreted by the clinician, and its true significance is unrecognized until at a later date the discovery of multiple abdominal cysts leads to a retrospective diagnosis. It is thus not uncommon for rupture of a visceral cyst to occur in youth, but for its clinical manifestations and recognition in the form of multiple abdominal cysts to be delayed until adult age is reached. Secondary abdominal cysts are always multiple, often irregular in shape and size, and owing to the relative tenuity of their adventitia, are prone to further ruptures with repetition of the above effects. As a result, the peritoneal cavity may become filled with hydatid cysts in all stages of development, a very grave condition aptly described as hydatidosis.

Usually the rent of the primary cyst becomes occluded by adhesions, and the residual germinal elements produce multiple daughter cysts, one type of localized secondary echinococcosis. It is a general rule that when multiple peritoneal cysts are found there is also a primary visceral cyst containing daughter cysts. Sometimes, of course, owing to the presence of a communication with a bile duct, intraperitoneal rupture of an hepatic cyst gives rise to leakage of the bile into the peritoneal cavity with the production of a choleperitoneum, often a puzzling condition.

Secondary cysts may also occur in the pleura or pericardium following rupture of a pulmonary or cardiac cyst.

*Metastatic Secondary Echinococcosis.*—This gives rise to the rarest but the most interesting type of all secondary cysts and is due to a rupture of a fertile simple cyst into the heart or venous system. The rupture may take place on the venous side of the circulation into peripheral veins or the right cardiac chambers, or into the arterial side when it takes place into one of the left cardiac chambers. Two sets of sequelae are possible. In both, of course, grave anaphylactic symptoms occur, although as a rule recovery from the primary rupture takes place. If the cyst ruptures into the venous side of the circulation, the scolices are carried through the right ventricle into the lungs, where they are filtered out and give rise to secondary pul-

monary cysts. These cysts are characterized by their multiplicity, their bilateral and peripheral distribution, and by their uniform size.

In the case of rupture into the left auricle or ventricle, the hydatid elements enter the systemic circulation and give rise to metastatic cysts in various parts of the body. Owing to the position and relative size of the carotid arteries, the majority of scolices are carried to the brain, which becomes the seat of the majority (60 to 70 per cent) of these secondary cysts. Some scolices, however, may escape



Fig. 3.—Multiple secondary cysts of the omentum, following intraperitoneal rupture of an hepatic cyst.

into the kidney, spleen, or liver. All these are simple cysts of approximately the same size, rarely becoming larger than a hen's egg.

These examples illustrate the classical manifestations of secondary echinococcosis, which is now clearly established as regards its etiology, pathology, and clinical aspects. It is a general rule, in the case of multiple cysts, that if the extrahepatic cysts are more than one-third of the total it is probable that they are secondary cysts.

#### MECHANICAL EFFECTS OF RUPTURE

The mechanical effects of rupture of a cyst are seen in cases of rupture into a natural channel. Following the initial flooding, which is



rarely serious, the passage of hydatid products along the channel leads to attacks of colic or intermittent, partial, or complete obstruction. These are immediate effects, although they may continue for months as fractional evacuation of the cyst contents occurs.

Microorganisms do not find their way through an intact laminated membrane, and in the case of simple cysts some degree of rupture of this membrane is an essential preliminary to suppuration. Once the hydatid membrane collapses, however, some serum is exuded into the cavity, and with hydatid debris makes such an excellent pabulum for the growth of microorganisms that when contact with a lining epithelium is made infection usually occurs. Small ducts may, how-



Fig. 4.—Multiple metastatic cysts of the brain, following left intracardiac rupture of a primary cardiac cyst.

ever, open into the cavity, and yet it may remain aseptic for years, and occasionally actual repair of the opening may occur. Obviously the time that elapses between rupture and infection depends on a great number of factors, so that although infection may coincide with the rupture, it is sometimes delayed for weeks or months.

*Rupture of Hepatic Cyst Into the Biliary Passages.*—As an hepatic cyst continues to enlarge, it often causes a quiet pressure necrosis of the wall of a large bile duct, and if the opening becomes large enough, some of the contents are forced into the duct. Such ruptures are relatively common, and I believe that some degree of intrabiliary rupture is the commonest complication of hepatic cysts. It may be a

quiet leak with the passage of fluid and small particles of débris, or a frank massive rupture with or without occlusion of the main ducts with daughter cysts. This rupture takes place most commonly in the intrahepatic portion of the ducts, the passage of material down the ducts being helped by intracystic pressure, diaphragmatic movement, and abdominal muscular action; and once started, the slippery, nonirritating membrane is helped on by the increased biliary flow after meals (Fig. 5).

In this way fractional evacuation of the cyst may take place into the duodenum. As is to be expected, this condition simulates complicated cholelithiasis very closely, this being the common diagnostic error. The following points are of interest in the differential diagnosis:

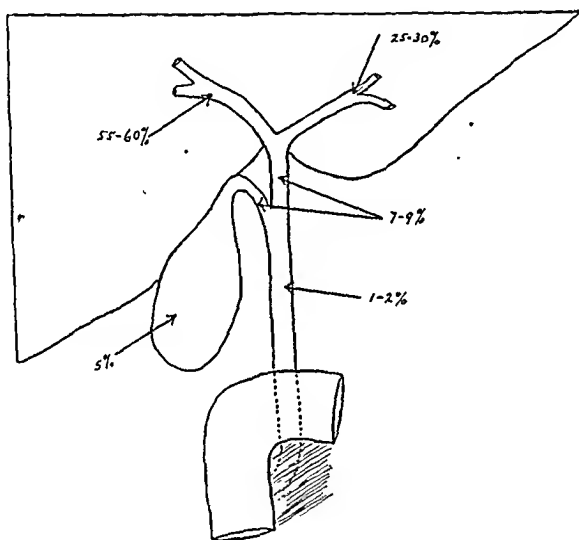


Fig. 5.—Figure showing sites of rupture of hepatic cysts into the biliary passages.

*Age.*—Hydatid disease tends to occur at a slightly younger age than stone in the common duct; i.e., thirty to forty years rather than forty-five to fifty-five years.

*Sex.*—In hydatid disease, males are affected as commonly as females; whereas, gallstone disease affects females four times as commonly as males.

*Pain.*—The pain of hydatid disease is not so severe as true gallstone colic.

*Previous History.*—In gallstone disease there is usually a long history of flatulence, etc.; this is often completely absent in hydatid disease.

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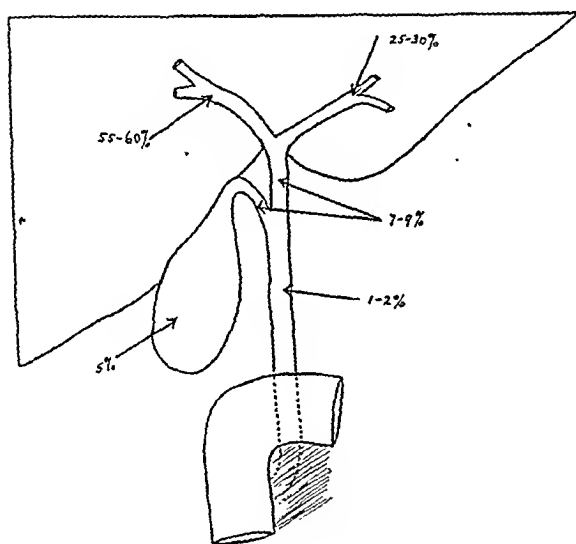


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*Previous History.*—In gallstone disease there is usually a long history of flatulence, etc.; this is often completely absent in hydatid disease.

*Examination of the Stools.*—Examination of the feces by washing should be used as a routine in all cases of jaundice. In hydatid disease the tough, bile-stained, laminated membrane, which resists putrefaction, is often discovered.

*Hepatomegaly.*—This is much commoner in hydatid disease than in cholelithiasis.

*Jaundice.*—A characteristic of hydatid disease involving the ducts present in 80 to 90 per cent of the cases. In gallstone disease gross persistent jaundice is rare and is practically confined to cases of stone in the common duct.

*Radiography.*—This should be applied as a routine, as it may indicate subdiaphragmatic distortion or calcareous change in a cyst.

*Immunological Reactions.*—These are of the utmost value. The use of the hydatid complement fixation test and the intradermal test of Casoni has revolutionized the diagnosis of hepatic hydatid in Australia.

#### HEPATOBRONCHIAL FISTULA

Hepatobronchial fistula is not uncommon and is due to rupture through the right diaphragmatic cupola by way of adhesions into the bronchus with or without pleural infection. The patient first expectorates daughter cysts and bile-stained debris, and later foul-smelling pus. All sorts of other complicated pictures due to other coexistent ruptures may occur, and unless the surgeon is alive to the vagaries of hydatid disease, mistakes in diagnosis, treatment, and prognosis are inevitable.<sup>1</sup>

#### OTHER TYPES OF RUPTURE

Rupture into the alimentary canal may also occur, occasionally with natural cure, although as a rule suppuration causes a rapid, grave alteration in the picture. Rupture into the urinary passage may occur in the case of renal or pelvic cysts with a close simulation of renal colic. This, too, is prone to infective sequelae.

*Rupture of a Pulmonary Cyst Into a Bronchus.*—This is the natural end of most pulmonary cysts, because by the time a cyst reaches a diameter of four to five inches it nearly always comes into contact with a large bronchus, the erosion of which causes a small part of the cyst wall to become unsupported. Following a cough, a muscular effort, an injury, or even spontaneously, the cyst wall gives way and the contents enter a bronchus. Rarely the patient is asphyxiated by the fluid or by the impaction of membrane in the glottis. More usually the dramatic symptoms are anaphylactic in nature.

After rupture the patient usually recovers rapidly, although for some time repeated expectorations of fluid and gradual evacuation of the cyst contents may occur. The patient may have attacks of coughing and hemoptysis, but remain afebrile and in good health throughout. Natural cure depends on the size of the cyst, as on it will depend the

thickness of the adventitia and the possibility of complete collapse and the time taken for disintegration and expectoration of the cyst wall. As is to be expected, small cysts and cysts in children more readily undergo natural cure. The larger the bronchial communication and the more dependent its position, the better are the chances of evacuation. Apical cysts are more likely to involve bronchi while yet small, and the opening will probably be dependent, facilitating drainage. Deeply placed parabronchial cysts also fulfill most of these conditions, and all are agreed that these should not be attacked surgically and that, if left alone, about 70 per cent will undergo natural cure. In some cases the cyst remains uninfected for long periods,

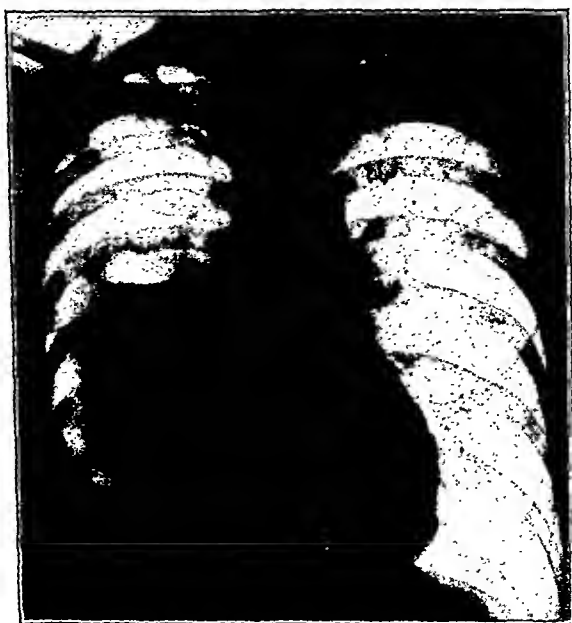


Fig. 6.—Echinococcus cyst of the right lung after rupture into a bronchus, showing hydatid pneumocyst.

while in others the presence of a fluid level with gas alone—hydatid pneumocyst—gives a very characteristic radiographic appearance (Fig. 6).

In a great many cases the cavity becomes infected, at first with saprophytic, but later with pathogenic, organisms, at first of low virulence, but later with virulent cocci and often anaerobic gas producers. The adventitia becomes thickened and lined on the inner aspect with a pyogenic membrane, and the clinical picture becomes one of intrapulmonary abscess, which necessitates surgical intervention.

*Hydatid Pneumothorax.*—Another interesting type of rupture is that of a subpleural pulmonary cyst into the pleural cavity. This may be

*Examination of the Stools.*—Examination of the feces by washing should be used as a routine in all cases of jaundice. In hydatid disease the tough, bile-stained, laminated membrane, which resists putrefaction, is often discovered.

*Hepatomegaly.*—This is much commoner in hydatid disease than in cholelithiasis.

*Jaundice.*—A characteristic of hydatid disease involving the ducts present in 80 to 90 per cent of the cases. In gallstone disease gross persistent jaundice is rare and is practically confined to cases of stone in the common duct.

*Radiography.*—This should be applied as a routine, as it may indicate subdiaphragmatic distortion or calcareous change in a cyst.

*Immunological Reactions.*—These are of the utmost value. The use of the hydatid complement fixation test and the intradermal test of Casoni has revolutionized the diagnosis of hepatic hydatid in Australia.

#### HEPATOBRONCHIAL FISTULA

Hepatobronchial fistula is not uncommon and is due to rupture through the right diaphragmatic eupola by way of adhesions into the bronchus with or without pleural infection. The patient first expectorates daughter cysts and bile-stained debris, and later foul-smelling pus. All sorts of other complicated pictures due to other coexistent ruptures may occur, and unless the surgeon is alive to the vagaries of hydatid disease, mistakes in diagnosis, treatment, and prognosis are inevitable.<sup>1</sup>

#### OTHER TYPES OF RUPTURE

Rupture into the alimentary canal may also occur, occasionally with natural cure, although as a rule suppuration causes a rapid, grave alteration in the picture. Rupture into the urinary passage may occur in the case of renal or pelvic cysts with a close simulation of renal colic. This, too, is prone to infective sequelae.

*Rupture of a Pulmonary Cyst Into a Bronchus.*—This is the natural end of most pulmonary cysts, because by the time a cyst reaches a diameter of four to five inches it nearly always comes into contact with a large bronchus, the erosion of which causes a small part of the cyst wall to become unsupported. Following a cough, a muscular effort, an injury, or even spontaneously, the cyst wall gives way and the contents enter a bronchus. Rarely the patient is asphyxiated by the fluid or by the impaction of membrane in the glottis. More usually the dramatic symptoms are anaphylactic in nature.

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test of Casoni has in our hands proved itself of the utmost value.<sup>3</sup> By the combined use of these methods, 90 per cent of hydatid cysts are now confidently diagnosed.

#### TREATMENT

*Simple Uncomplicated Cysts of the Liver.*—As a rule general anesthesia is indicated as there seems to be some risk of anaphylactic shock, if by chance fluid is spilled and absorbed, when local anesthetic is used. The incision should be made to give the most direct approach. In the case of cysts of the upper quadrant, the transcostal route must be used, but in order to lessen the ever present risk of pleural contamination, the incision should be made as far forward and as low down as possible to avoid the pleura. If this cannot be done, a two-stage procedure with preliminary packing to produce adhesions is advisable.

The field should be well packed off and it is important to realize that scolices spilled into the wound may implant and recur; in other words, the cyst must be treated as an infective focus. Guy sutures should be inserted, and after partial evacuation with a needle, commercial formalin should be injected in sufficient quantity that when mixed with the fluid of the cyst it will form a 2 per cent solution. This, if allowed to act for three or four minutes, will sterilize the scolices and the cyst can then be widely opened and evacuated with the pump. If daughter cysts are present, it is impossible to sterilize the contents with formalin, but this should be used after evacuation to swab out the cavity and so kill any free scolices. After evacuating and cleaning the cavity, the procedure varies with the state of the cyst. If clean, it should be filled with saline solution and closed completely without drainage. If full of debris, if bile stained, or if there is any suspicion of infection, it should be partly sutured and drained by a wide tube using omentum if possible to protect the suture line and the tube.

Cysts which have involved the biliary passages introduce difficult problems depending on the pathologic condition found. If there is obstructive jaundice, the common duct must be opened and the hydatid debris evacuated while the offending cyst must also be found, and as there is nearly always infection present, both it and the ducts must be drained.

Suppurating cysts in the liver must be treated by open drainage in exactly the same way as hepatic or subphrenic abscesses, both of which conditions it may simulate.

For fuller details of the various problems in the treatment of these cases, reference should be made to references 4, 5, and 6.

*Pulmonary Cysts.*—Parabronchial cysts which are normally small and inaccessible and which from their position have an excellent chance



comparatively quiet, with immediate anaphylactic symptoms or the formation later of secondary pleural cysts.

As a rule, however, the subpleural cyst is large enough to have also involved a patent bronchus, in which case a pneumothorax follows. Hydatid pneumothorax, occurring as it does in a previously healthy patient, may be most dramatic. At first the effect is mechanical, although the mild irritation of the pleura often leads to a hydropneumothorax. In the majority of cases, however, infection leads to a pyopneumothorax.

This condition may be confused with tuberculous pneumothorax, but unlike that disease it is common in adolescents, more common on the right side; there is rarely any suggestive previous history; no signs are present on the opposite side; tubercle bacilli are absent from the sputum; anaphylactic symptoms are common; and the typical hydatid immunologic reactions are often positive.

*Death of the Parasite.*—Following aseptic rupture into a natural channel and occasionally apparently from unknown causes, the parasitic fluid may be evacuated or absorbed, the parasite dies, and a collection of inspissated material containing cholesterol, fatty acids, calcium salts, and crumpled hydatid membrane is left. This becomes enclosed by fibrous tissue which contracts and often shows calcareous deposition. Such dead cysts are not infrequently found at autopsy.

*Suppuration.*—Suppuration is a constant risk in all cases in which rupture into a natural channel has taken place. This is particularly prone to occur in the cysts which have ruptured into the bronchi or the biliary passages. It may be for long delayed, but unless complete evacuation through a relatively dependent opening takes place, the hydatid debris and serum make such an excellent pabulum for bacterial growth that suppuration is always likely to occur. When it does, the patient exhibits signs and symptoms typical of an abscess of the region involved, with a rapid alteration of the clinical picture.

#### DIAGNOSTIC METHODS

Radiography has revolutionized the diagnosing of intrapulmonary cysts, since the saline cystic contents are relatively opaque and give a characteristic shadow. In subdiaphragmatic cysts, elevation of the diaphragm is a very striking feature and can often be detected. Calcareous changes in the adventitia are also often noted in the case of abdominal cysts. Routine x-ray examination alone, however helpful it may be in pulmonary cases, often fails in young subjects with cysts of a moderate size; and in Australia this method of examination is always supplemented by immunologic methods. The precipitin test, as utilized by Fleig and Lisboune, has given way to the complement fixation test as modified by Fairley,<sup>2</sup> using fresh hydatid fluid from sterile sheep cysts as antigen. In addition, the intradermal

## MALIGNANT TUMORS OF THE THROAT

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IN SEPTEMBER, 1931, Henri Coutard<sup>1</sup> presented before the American Roentgen Ray Society a résumé of his excellent results obtained with the roentgen treatment of epitheliomas of the tonsillar region, hypopharynx, and larynx at the Curie Institute in Paris. His method was radically different from those previously used in this country since he advocated the administration of doses to the sides of the neck and the deep tissues of the throat equal to five or six times those formerly thought to be safe for the normal tissues. Severe reactions consisting of desquamation and ulceration of the superficial structures both inside and outside the pharynx were obtained, but when the massive doses were properly fractionated and given in small daily amounts over periods of three to five weeks, prompt healing of the roentgen sequelae occurred, and in many instances the malignant tumors melted away never to recur. Good results had been obtained in the United States with radium, but its proper application, particularly in the more inaccessible lesions, was difficult and often impossible and the simpler, more efficient x-ray technique was welcomed by American radiologists.

### PATHOLOGY

For the sake of simplicity, malignancies of the throat will be designated in this paper as tumors of the pharynx, including those arising from the soft palate, the tonsils, base of the tongue, lateral pharyngeal walls, pyriform sinuses, edges of the epiglottis, and upper margins of the larynx; and intrinsic tumors of the larynx, including those arising from the ventricular folds, vocal cords, arytenoids, and walls of the larynx below the vocal cords. All of these neoplasms are particularly well suited for radiation therapy because their radiosensitivity in most instances exceeds that indicated by the histologic picture. In 1927, Quick and Cutler<sup>3</sup> described the marked radiosensitiveness of transitional cell carcinoma of the pharynx, and in 1929, Ewing<sup>2</sup> indicated that lymphoepithelioma responded even better. Martin and Pflueger,<sup>4</sup> after carefully studying a mixed group of cases, found that epidermoid carcinomas and even adenocarcinomas of the pharynx could be eradicated with doses much smaller than those needed for similar lesions in other portions of the body, and the ready response of lymphosarcoma has been known for years. Caldwell<sup>5</sup> and others feel that reticulum cell sarcoma, a very rare

of natural cure by expectoration through a bronchus should be left alone unless some complication such as persistent infection occurs.

All peripheral cysts should be operated upon, because complications such as intrabronchial or intrapleural rupture are, owing to the impossibility of natural cure and to the spread of infection, much more dangerous. As a rule in clean cases there are no pleural adhesions, and the ever present risk is that of pleural soiling. In these cases a two-stage operation with preliminary excision of part of the chest wall after careful localization and tamponade for twelve days, followed by incision, evacuation, and drainage, is a safe and eminently satisfactory procedure. This may be performed under local or general anesthesia with the patient in such a position as to lessen the risk of sudden bronchial flooding, a risk which is always present. Positive pressure intratracheal anesthesia can also be used in these cases, but calls for some manual dexterity in putting in holding sutures to prevent pleural soiling, and close cooperation with the anesthetist who must expand the lung to obliterate the pleural cavity. All of these cases should be drained by means of a wick of rubber tissue for a few days to obviate the risk of surgical emphysema or valvular pneumothorax.

In cases of intrabronchial rupture there is always some degree of infection and the risks of pleural contamination are greatly increased. These should be treated as one would a pulmonary abscess, and after careful localization a two-stage operation is always advisable.

For a fuller discussion of these and allied problems the reader is referred to reference 1.

I am indebted to the editor of the Medical Journal of Australia for permission to reproduce Figs. 1, 3, 4, and 5.

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vious, but they also have the following disadvantages which, although they were noted in a previous article,<sup>13</sup> may bear repetition:

1. The walls are only 0.3 mm. thick and allow some of the more irritating rays to pass through.
2. It is difficult to plant such small structures in regular patterns in inaccessible locations.
3. They may slip out of place in the throat and be aspirated, thereby producing a lung abscess.
4. They may produce a necrosis of the cartilage if placed in contact with the epiglottis or other cartilaginous structures of the larynx.
5. They sometimes set up a neuritis producing constant headache about the ear when planted in the upper lateral pharynx.
6. They are expensive and can be obtained only from New York City by those of us who are located in the more remote districts.

In the more accessible lesions, particularly the metastatic nodes in the neck, we have found it advantageous to use Cade's modification of the weak, heavily filtered radium element needles devised by Regaud. The advantages and disadvantages of these needles are described in a previous article.<sup>14</sup>

The results reported by Coutard intrigued the interest of American radiologists immediately, but his plan necessitated the use of an expensive piece of x-ray apparatus for as much as one to four hours daily over periods of three or four weeks on a single patient, and such uneconomical operation could hardly be advocated for a busy clinic. Most of the workers in this country decreased the daily treatment time by reducing the filtration and increasing the voltage and tube current. Although the French method required the use of a filter of 2.0 mm. of zinc, we published data<sup>15</sup> in 1935 indicating that a total dose of 3,600 roentgens (measured in air without backscattering) could completely eradicate a large epidermoid carcinoma, grade III, of the skin of the face when given in twelve equal daily doses with a filter of 0.75 mm. of copper and 1.0 mm. of aluminum. With a kilovoltage of 200, a tube current of 6.0 ma., and a target skin distance of 50 cm., the daily dose could be given in twenty-five minutes. More recently the work of Merritt and Rathbone has convinced us that the skin reactions can be lessened by an increased filtration. By increasing the kilovoltage to 220 and the tube current to 20 ma., it is possible to give a daily dose of 300 roentgens in twenty minutes with a filter of 0.8 mm. of tin, 0.25 mm. of copper, and 1.0 mm. of aluminum, the so-called heavy Thoreaus filter, which is considerably heavier than the one recommended by Coutard himself. A rather limited experience with this technique has led us to adopt it for all work about the throat and neck, but the recent rapid progress in roentgen therapy may cause us to change it before this article appears in print.

tumor in the throat, should not be included in the lymphosarcoma group, but from the clinical point of view the treatment and results are identical. Clerf and Crawford<sup>6</sup> have shown that 98 per cent of the intrinsic malignant neoplasms of the larynx are squamous cell carcinomas. The remainder are usually adenocarcinomas, and it has been our experience that both of these types can be favorably influenced with relative ease. Although most of the tumors just enumerated can be graded according to Broder's classification, Cade,<sup>7</sup> Cutler,<sup>8</sup> Garland,<sup>9</sup> and Martin<sup>10</sup> have independently observed that their response does not correspond to their theoretical radiosensitivity based on the histologic findings; and Quick<sup>11</sup> has especially emphasized the fact that two tumors having exactly the same appearance under the microscope may react differently to identical doses of radiation. In no other portion of the body is one so strongly impressed with the fact that prognosis should never be based on the microscopic report alone.

#### METHOD OF TREATMENT

When the value of radium was first recognized, it was placed in thin-walled steel needles in rather large quantities and the needles were inserted into the diseased tissue for varying periods of time. When efficient doses were used, painful sloughs were likely to occur and carcinoma often continued to grow outside the treated areas. Surface applications were also made with radium plaques and capsules, but it was found difficult to control the deeper extensions of the disease in this manner. As a result of much experimentation, Regaud and his collaborators at the Curie Institute elaborated certain principles which served to markedly increase the efficacy of irradiation. It was their observation that the least damage resulted in normal tissues and that the rays showed their greatest selectivity for malignant cells when very low intensities, short wave lengths, and relatively long periods of continuous treatment were utilized. In this country an attempt was made to carry out these principles by inserting small bits of capillary glass tubing containing radon directly into the tumors. Since the radon rapidly lost its power to emit rays, it was found safe to leave these small foreign bodies in place. However, the glass possessed very little filtering power, and although the intensity was low and the time of treatment prolonged, the long wave lengths passing through the glass produced many painful sloughing reactions. In 1926, Failla<sup>12</sup> described similar implants made from capillary gold tubing having a wall thickness of 0.3 mm. which served to remedy this fault to a large extent. These applicators are very small and can be inserted through specially constructed trocars into most of the growths occurring in the pharynx and larynx. Their advantages over radium element needles for this kind of work are ob-

When the radioepithelitis is at its height, the malignant process melts down rapidly and in the successful cases healing occurs within a week or two, leaving the mucous membranes practically normal in appearance. The skin heals more slowly, but when the dosage has been carefully computed, the end-results are excellent and little external evidence of the treatment remains. The entire process usually requires from six to eight weeks for its consummation. Hayes Martin observes his cases frequently during the healing stages and feels free to insert radon implants into any malignant areas which do not show a satisfactory regression. This procedure is rarely necessary except in the metastatic areas in the neck.

With the onset of the pharyngeal irritation, feeding becomes increasingly difficult. The basis of the diet is milk containing beaten raw eggs, a little orange juice, and malted milk. To this is added cereals, ice cream, creamed soups, puréed vegetables, and any soft foods that the patient will take. Occasionally it is necessary to use a nasal tube for a few days. Swallowing is made somewhat easier by allowing an aspirin tablet to dissolve in the mouth before each meal. A 5 per cent sodium bicarbonate solution is of some value in keeping the mouth and throat clean between meals. Simple soothing applications, such as borie ointment, are all that is needed for the skin reactions. For ten days to two weeks these patients may have a slight temperature elevation. They are quite uncomfortable and usually lose from ten to fifteen pounds. It is essential that they receive vigorous encouragement daily, since they become convinced that the malignant process is progressing and various forms of mental depression are often observed. Fortunately, the radiation effects subside rapidly, and when improvement begins, it progresses with a speed which fully justifies the severity of the treatment.

#### METASTASES

The metastases of carcinoma of the pharynx and of the intrinsic larynx present entirely different problems, because the laryngeal tumors spread slowly and usually produce symptoms such as hoarseness, cough, dyspnea, pain, or hemoptysis long before extension occurs. For this reason larynx patients are likely to come for treatment early. When metastases do occur, they appear in the adjoining tissues and lymph nodes of the neck, and their appearance taken with the history makes the diagnosis evident. Obstruction of the larynx which often requires the immediate insertion of a tracheotomy tube is the most troublesome complication encountered.

In many instances, pharyngeal malignancies produce so few symptoms that the victims consult a physician only after the manifestations of secondary extensions appear. This is particularly true when the primary growth is located well up in the lateral pharynx. Three such cases have appeared in our clinic with a diagnosis of Hodgkin's disease because of

In general, our x-ray technique, with the exception of the selection of a filter, follows that recommended by Martin and McNatin.<sup>17</sup> Areas large enough to cover the primary lesion in the throat and its probable immediate paths of extension are mapped out on either side of the neck. They may be circular or square and usually measure from 7.0 cm. to 15.0 cm. in diameter or in width, as the case may be. It is desirable to keep these areas as small as possible in order that the reactions in the normal tissues may be reduced to a minimum. The treatments are given through cones of the size and shape of the mapped-out areas. They are attached to an oil-cooled, shockproof tube holder and may be placed in intimate contact with the skin without danger of electrical shock or even of static discharge.

Usually 300 roentgens measured in air without backscattering are given daily (except Sunday) to alternate sides of the neck. In most instances each skin area receives a total dose varying from 3,000 r. to 3,600 r. When the patient responds poorly, it is often advisable to reduce the daily dose, and in some instances the total dose has been lowered with a favorable outcome. With tumors located on one side of the throat, it has sometimes seemed wise to apply two-thirds of the dose to the affected side and one-third to the other side in an effort to save the function of the salivary glands on the normal side. Coutard states that the cancericidal dose for tumors of the mucous membranes of the throat is about 3,500 r. with backscattering and this should amount to approximately 2,625 r. without backscattering. Treatment should never be stopped until at least this much irradiation as calculated from penetration charts has been delivered to the affected region, and we usually give a minimum of 3,000 r. unless the reaction produced is very severe. In most instances the series is completed during a period of twenty-four to twenty-eight days.

In seven to nine days after the first dose, the patient begins to complain of a sore throat, dryness of the mouth, and difficulty in swallowing. Inspection at or near this time reveals spots of superficial ulceration and the formation of a white membrane on the uvula and anterior pillars. During the next week this reaction appears on the posterior pharyngeal wall, floor of the mouth, insides of the cheeks, epiglottis, base of the tongue, and eventually on the vocal cords and dorsal surface of the tongue. The saliva becomes thick and stringy and the patient finds clearing his throat difficult. The term radioepithelitis is used by Coutard to describe these changes in the mucous membranes.

Near the end of the series of treatments, the irradiated skin takes on a dusky red color. The surface then peels off and large, moist patches which are completely denuded may appear. The use of very heavy filters has in our opinion decreased the degree of denudation. Radioepidermitis is the term applied by Coutard to this skin change.

if the invasion is recent, and we have seen strabismus, ptosis of the upper lid, partial blindness, and pain in the face and ear clear up completely following irradiation of the side of the skull.

#### RESULTS OF TREATMENT

In evaluating a new method, the results produced must be carefully compared with those accredited to time-honored surgical procedures. New<sup>20</sup> says: "It is generally recognized that surgery offers little in cases of malignant tumors of the nasopharynx"; and Bloodgood states in *Lewis' Practice of Surgery* that he has been unable to cure cancer of the tonsil with the cautery or with diathermy. Patterson<sup>21</sup> reports 9 successes out of 41 cases of cancer of the tonsil and fauces treated with the endothermy knife. Certainly this degree of success can be obtained only in the very early stages of the disease. When the primary lesion is large and extension has occurred, surgical procedures frequently do little more than add to the patient's discomfort. Reference to Table I, which includes all of our patients treated a year or more ago, shows that all of the cases of pharyngeal carcinoma in our small series obtained a complete regression of the primary tumor and marked improvement appeared in the neighboring extensions even in advanced stages of the disease. Death, when it occurred, resulted from complications or distant metastases. The immediate improvement in the patient's condition was very striking in every instance. Our experience has not extended over a period of five years as yet, but Coutard reported 23 per cent of 46 cases of carcinoma of the tonsil, and 10 per cent of 89 cases of carcinoma of the hypopharynx free of symptoms for a period of five years. Lenz, Coakley, and Stout,<sup>22</sup> using a technique very similar to Coutard's, report 6 cases of cancer of the tonsil and base of the tongue well for periods varying from nine months to two years. Hayes Martin, who uses low filtration to obtain a high x-ray intensity and who inserts radon seeds into stubborn areas, reports 24 per cent of 41 cases of cancer of the tonsil, 35 per cent of 21 cases of cancer of the nasopharynx, and 22 per cent of 9 cases of cancer of the pharynx and soft palate well for periods of one and one-half to three and one-half years. These figures strongly support irradiation as the method of choice in all malignant tumors of the pharynx.

In carcinoma of the intrinsic larynx, a much stronger case can be made out for surgery. New and Waugh<sup>23</sup> report 69 cases out of 135 operated on at the Mayo Clinic free of carcinoma at the end of five years. These authors do not give the number of inoperable cases in their series. However, since the radiologist treats all of the patients applying for treatment, his statistics must be compared with absolute surgical figures if a fair comparison is to be made. Mullin and Darsie<sup>24</sup> found only 54 per cent of 133 cases in their clinic to be operable and we may assume, therefore, that New and Waugh obtained five-year cures in 69 cases out



the large masses of painless glands discovered in the sides of the neck. In the presence of cervical adenopathy, we routinely order a blood examination and a careful examination of the throat before considering the surgical removal of a gland for microscopic study. Carcinoma of the throat occurs with surprising frequency in young individuals and the youthfulness of the patient should never be considered as a point in favor of the diagnosis of lymphoblastoma.

Intracranial nerve involvement as a first symptom of cancer of the pharynx is not at all uncommon. Hansel<sup>18</sup> has recently reported a group of these cases in detail. Every nerve on the affected side except the eighth is sometimes paralyzed. This freedom of the auditory nerve is accounted for by the fact that most of the pressure is exerted by growths of the tumor outside of the cranial cavity and only the eighth nerve fails to pass out through one of the foramina in the base of the skull. After pharyngeal carcinoma invades the neighboring tissues, it often causes deafness and tinnitus by blocking the eustachian tube and fixation of the jaw by invasion of the pterygoid and masseter muscles. Upward extension produces invasion of the sphenoids, and at times the sella turcica is partially destroyed. The earliest cranial nerve involvement follows extension of tumor tissue into the sphenoid fissure and an internal strabismus produced by pressure on the sixth nerve, which lies lowest in the fissure, is the first noticeable clinical sign. Pain in the eye, side of the face, and ear from fifth nerve pressure usually appears next and may be followed by blindness from optic atrophy. Other symptoms observed in these cases are facial paralysis, the jugular foramen syndrome, toothache, earache, pain in the tongue, neck and shoulders, exophthalmus, dysphagia, aphonia, hoarseness, dizziness, and contracted visual fields. Every patient with a progressive involvement of intracranial nerves is entitled to a careful examination of the nasopharynx. Good x-ray films of the base of the skull will, at times, show definite erosion of bone about the sella turcica and the foramina for the nerves.

The more embryonic tumors of the upper pharynx spread rapidly to other portions of the body and metastases eventually appear in the mediastinum, lungs, and abdomen. Cappell<sup>19</sup> states that the lymphoepitheliomas usually involve the spine near the termination of the disease.

In primary laryngeal cases, it is sufficient to include the adjoining soft tissues and glands within a 3.5 cm. radius of the center of the larynx in the treated area. However, the pharynx, anterior half of the floor of the skull, and cervical region should be irradiated in dealing with pharyngeal carcinoma, even when no metastases can be demonstrated. Many of the distant recurrences can be dealt with successfully, but it has not been found practical to administer heavy doses to the entire body and therefore no cures are recorded. Definite improvement in paralyzed cranial nerves results from treatment of the base of the skull

TABLE I--CONT'D  
*Carcinoma of Pharynx*

AGE	PRIMARY LESION	PATHOLOGY	METASTASES	DOSAGE	TREATMENT	RESULTS
62	Base of tongue and pharynx	Transitional cell grade 3	None	2,700 r. lt. 1,900 r. rt.	17 days	Free of disease 1 yr. and 10 mo.
54	Rt. tonsil and lateral pharynx	Epidermoid carcinoma grade 3	Node in rt. neck	2,700 r. rt. 1,800 r. lt.	16 days	Free of disease 1 yr. and 1 mo.
58	Left upper pharynx	Transitional cell carcinoma	Large mass in left neck	3,900 r. lt. cheek 4,435 mg. hr. in neck	12 days	Free of disease 2 yr. and 6 mo.
64	Right pharynx	No tissue	Large node in neck	3,100 r. rt. neck 1,750 r. lt. neck	21 days	Free of disease 1 yr.
70	Pharynx and nose	Transitional cell grade 3	Neck Mediastinum Abdomen	2,950 r. lt. 2,950 r. rt.	24 days	Died of metastases after 5 mo. Throat clear of disease
45	Rt. pharynx and epiglottis	Epidermoid carcinoma grade 3	Many glands right neck	3,900 r. rt. neck	15 days	Died of metastases after 9 mo. Throat clear of disease
34	Rt. pharynx	Transitional cell grade 4	Mass in rt. neck	3,900 r. rt. neck	14 days	Throat clear. Small node in neck after 1 yr. 6 mo.
50	Rt. pharynx	Lymphoepithelioma	Neck, lung Mediastinum Abdomen	2,300 r. rt. neck 1,500 r. ant. chest 1,500 r. post. chest	30 days	Died of metastases after 4 mo. with throat, chest, and neck clear

TABLE I  
RÉSUMÉ OF DATA COVERING CASES OF CARCINOMA OF THE THROAT TREATED IN OUR LABORATORY MORE THAN ONE YEAR AGO  
*Intrinsic Carcinoma of the Larynx*

AGE	PRIMARY LESION	PATHOLOGY	METASTASES	DOSAGE	TREATMENT	RESULTS
58	Upper larynx obliterated	Epidermoid carcinoma	None	3,000 r. rt. 3,000 r. lt.	22 days	Free of disease 2 yr. and 1 mo.
50	Posterior rt. vocal cord	Epidermoid carcinoma grade 2	None	3,000 r. rt. 3,000 r. lt.	22 days	Free of disease 1 yr. and 5 mo.
55	Most of left vocal cord	Epidermoid carcinoma grade 1	None	2,700 r. lt. 1,200 r. rt.	14 days	Free of disease after 4 yr. and 3 mo.
53	Mass beneath ant. commissure	Epidermoid carcinoma grade 2	None	3,000 r. rt. 3,000 r. lt.	23 days	Free of disease after 4 yr. and 5 mo.
65	Left cord and arytenoids	Epidermoid carcinoma grade 3	None	3,000 r. rt. 3,000 r. lt.	22 days	Free of disease 1 yr. and 8 mo.
64	Rt. arytenoid	Epidermoid carcinoma grade 2	None	3,000 r. rt. 3,000 r. lt.	23 days	Free of disease 1 yr.
67	Rt. epiglottis and larynx	No tissue	Many cervical glands involved	3,000 r. rt. 3,000 r. lt.	14 days	Free of disease 1 yr.
56	Upper larynx obliterated	Adenocarcinoma grade 2	None	3,000 r. rt. 3,000 r. lt.	22 days	Died of lung abscess after 2 mo. No cancer found at autopsy
66	Ventricular folds and thyroid cartilage	Epidermoid carcinoma grade 2	Tissues about larynx	3,125 r. rt. 3,000 r. lt.	24 days	Local recurrence after 1 yr.

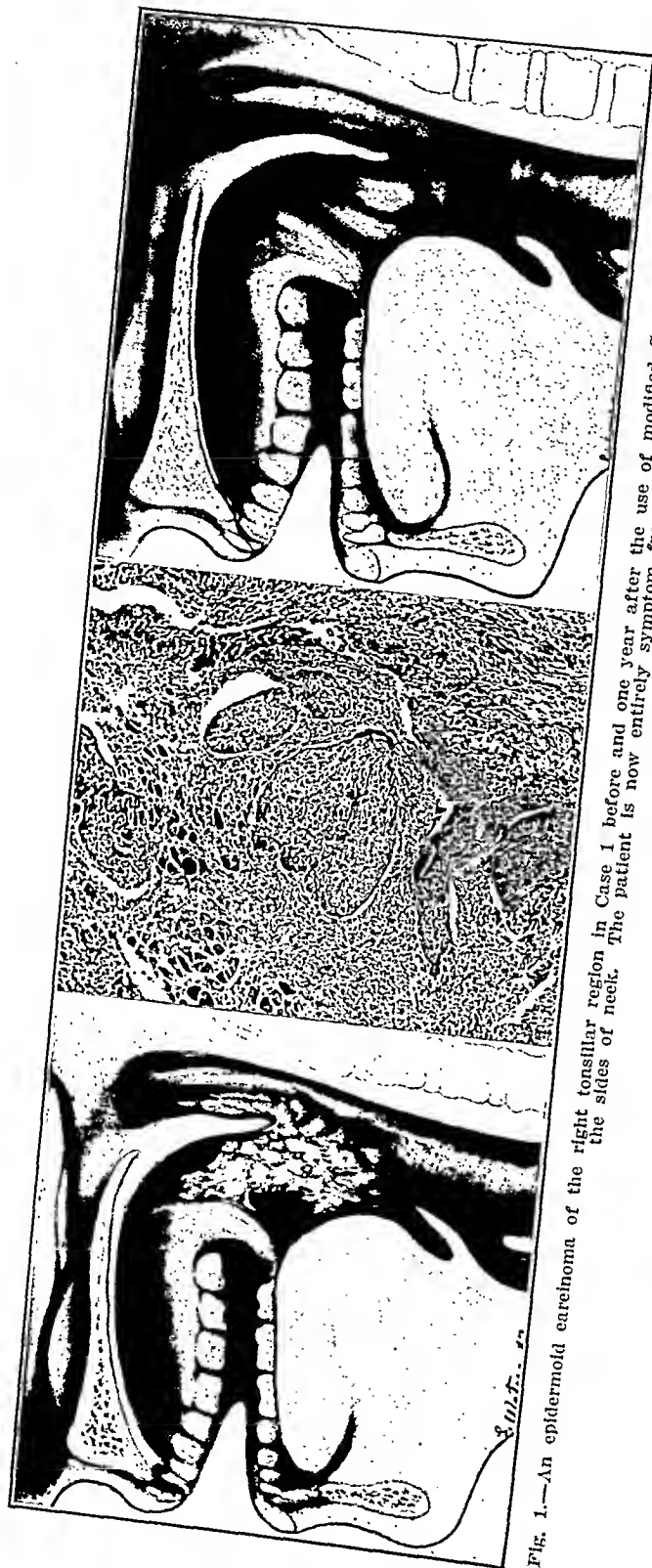


FIG. 1.—An epidermoid carcinoma of the right tonsillar region in Case 1 before and one year after the use of modified Coutard x-ray therapy over the sides of neck. The patient is now entirely symptom free.

of a total of approximately 250 patients. If we accept this theoretical figure, they obtained 27.6 per cent absolute cures in their series. Coutard reports 21 per cent of five-year cures in his series of 60 irradiated cases and these figures suggest that ultimate results are similar for the two methods. Lenz, Coakley, and Stout report 5 cases out of 11 free of disease for periods varying from nine months to two years. And Martin and McNatin report 3 of 4 cases of carcinoma of the intrinsic larynx clear of disease for periods varying from nine months to two and one-half years. In our own clinic, 6 cases out of 9 have remained free of disease for periods varying from one year to four years and three months.

Assuming that the chance of cure is about the same with the two methods, it would seem at first glance that there is little choice between them. However, New and Waugh found it necessary to do a laryngectomy in 44 per cent of their cases who were thereby deprived of any possible future use of the vocal cords and who were also condemned to the use of tracheotomy tubes for the remainder of their lives. Although a thyrotomy was done in the others, they could not be assured of a useful voice. It is true that rather complicated mechanical devices have been used successfully for speaking, but normal use of the trachea for speaking and breathing is highly desirable. Although tracheotomy tubes were used temporarily in three of our worst cases, it was found necessary to leave the tube in place permanently in only one case. All of our other successful cases obtained a usable voice, although many of them could only speak in a whisper when the treatment was started. When all of these facts are taken into consideration, it is our feeling that irradiation should be the method of choice even in the early cases. If regression is not complete, operative procedures can always be carried out at a later date. New and Waugh observed that they obtained no operative cures in cases having grade IV epidermoid carcinomas and for this reason surgeons who still favor the operative methods should treat only the tumors having a low histologic grading. We feel very definitely that inoperable patients as well as those on the borderline should receive irradiation because they almost always obtain some degree of improvement and surgical procedures frequently make them very much worse.

The following case histories have been selected because they show that malignant tumors of the pharynx and larynx can be eradicated with the external use of x-rays alone and they also indicate that the pathologic histology makes little difference in the ultimate response of the primary growth:

CASE 1.—A white woman, fifty-four years of age, began to have attacks of discomfort in the right side of the throat ten months before admission. Her physician told her that she was suffering from a recurrent tonsillitis and minimized the importance of the condition. Seven months later a gland appeared beneath the angle of the right jaw and swallowing became painful. One week before admission another physician discovered a tumor in her throat.

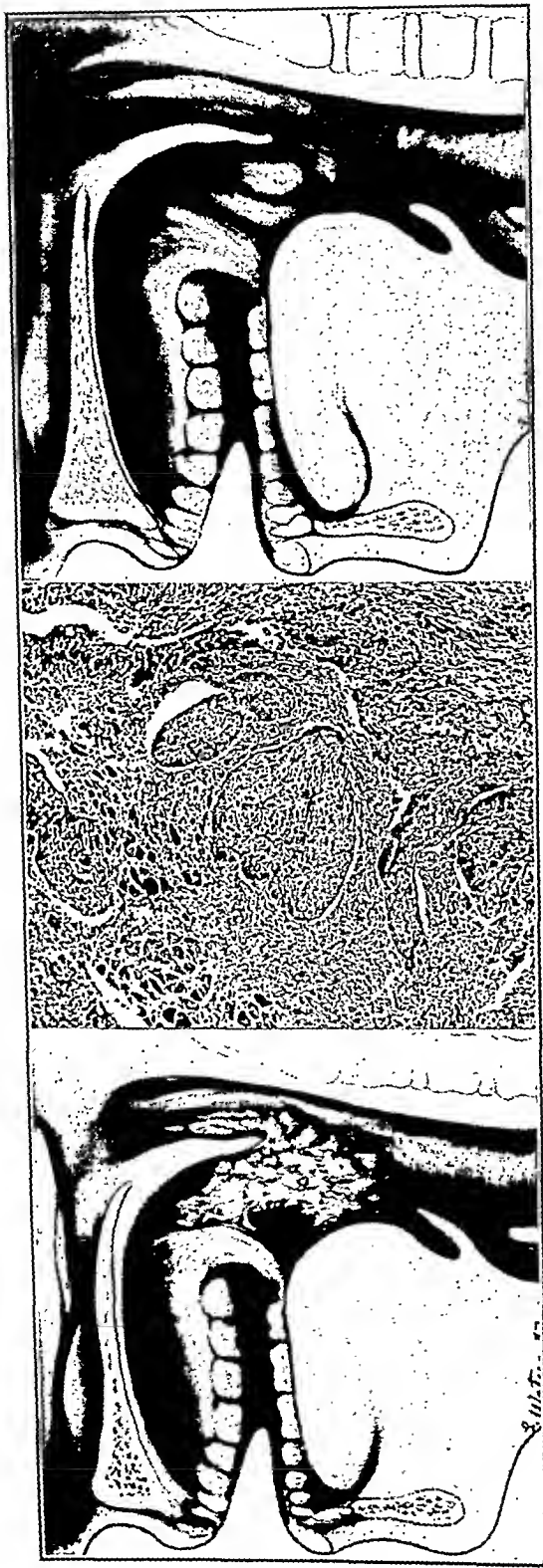


Fig. 1.—An epidermoid carcinoma of the right tonsillar region in Case 1 before and one year after the use of modified Coutard x-ray therapy over the sites of neck. The patient is now entirely symptom free.

At admission a flat tumor with a friable surface was seen to extend from the right anterior pillar backward across the tonsillar area onto the pharyngeal wall. This growth measured one and one-half inches in diameter. The histologic diagnosis was epidermoid carcinoma, grade III. A single gland beneath the angle of the right jaw measured one inch in diameter.

During a period of sixteen days, 2,700 r. (measured in air without backscattering) were administered on the right side of the neck to a square area measuring 10 cm. on a side, and 1,800 r. were given through a circular port measuring 7 cm. in diameter on the left side. Three hundred roentgens were given each day with 220 kv., a target skin distance of 50 cm., and a filter of 2.0 mm. of copper and 1.0 mm. of aluminum. The current through the tube was 20 ma.

By the sixteenth day she had developed such a severe epithelitis that it seemed wise to discontinue treatment. She returned on the twenty-sixth day after the series was completed; at which time the tumor in the throat had disappeared leaving the mucous membrane smooth and normal in appearance. The gland was reduced to less than half its former size. After thirty-three more days had elapsed, no gland could be palpated, but she complained of a dry throat and a tenacious sputum. She has remained entirely well with no evidence of a recurrence for one year and three months.

CASE 2.—A white woman, sixty-five years of age, came to the hospital complaining of soreness in the left side of her throat of about a month's duration. Four years previously some sort of gland of unknown origin was removed from the left side of the neck. Seven months before admission a large swelling appeared in the left side of the neck, but it gradually subsided. The treatment consisted solely of cold applications and rest. She became alarmed recently when she discovered a tumor in the region of the left tonsil.

Examination revealed an irregular tumor mass with a friable surface measuring one and one-fourth inches in diameter replacing the left tonsil. Nothing abnormal was felt in the neck except a small node well down in its midportion on the left side. A piece of the tumor was removed and diagnosed as lymphosarcoma by Dr. George Caldwell. Doses of 2,700 r. on the left side and 1,500 r. on the right side were delivered to the pharynx through square ports measuring 10.0 cm. on a side. The daily dose was 300 r.; the kilovoltage, 220; the filtration, 0.8 mm. of tin, 0.25 mm. of copper, and 1.0 mm. of aluminum; the distance 50 cm.; and the current 20.0 ma. On the fifth day of treatment the tumor had completely disappeared. An examination done after six weeks revealed no evidence of malignancy in the throat, neck, or chest. Although she had a rather severe reaction, both inside the pharynx and over the skin of the left side of the neck, it subsided rapidly, leaving no sequelae except some dryness of the mouth and a disturbed sense of taste.

CASE 3.—A colored boy, nineteen years old, was brought to the hospital because of hemorrhages from his nose during a period of seven weeks. For about six weeks, glands had been growing rapidly in both sides of his neck. For one week he had found it very difficult to open his mouth or to chew because of pain in the cheeks and limited motion of the lower jaw.

At admission he looked quite ill and was slender and poorly nourished. Large masses of glands were palpable on both sides of the neck. Dr. Lyle Sellars reported a large mass of malignant tissue filling the upper portion of the nasopharynx and extending into the nasal passage. He removed a specimen which was diagnosed as transitional cell carcinoma, grade III.

Areas measuring 15.0 cm. on a side were laid out to include the cheek, pharynx, anterior half of the base of the skull, and neck on each side of the head. Each area received 2,950 r. given during a period of twenty-four days. The treatment factors

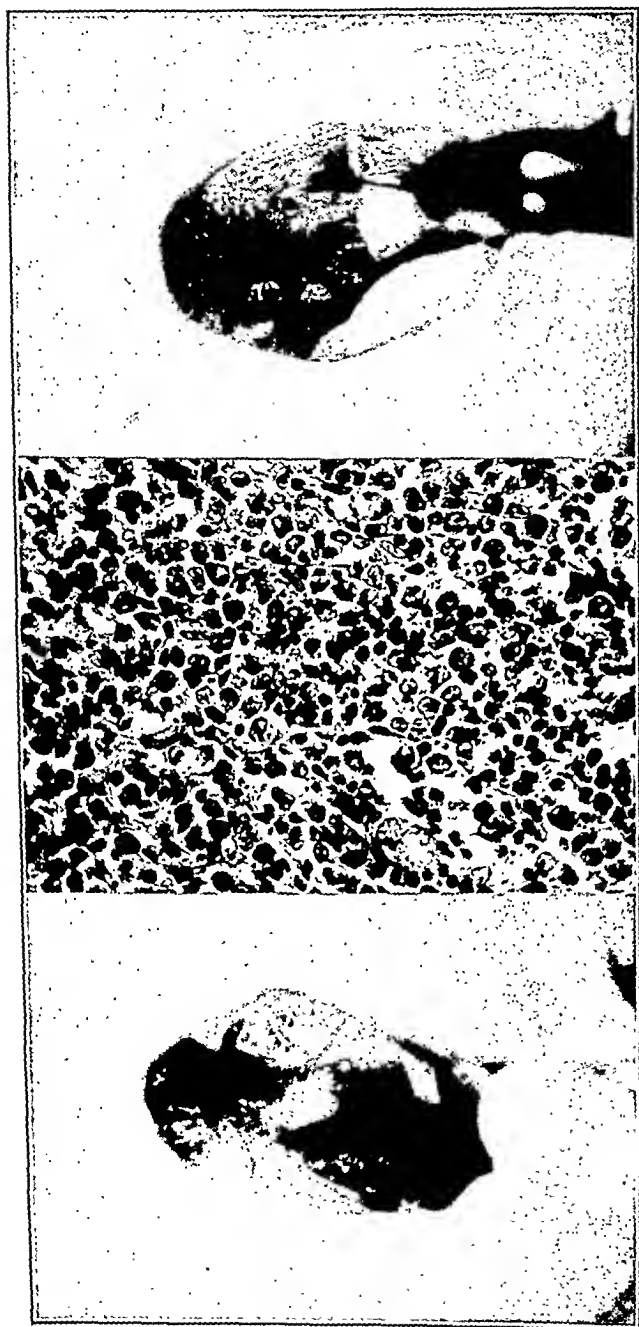


Fig. 2.—Large lymphosarcoma of the left tonsil before and five days after beginning a modified series of Coutard x-ray treatments over the sides of the neck in Case 2. No evidence of the disease is made out at the end of six weeks.



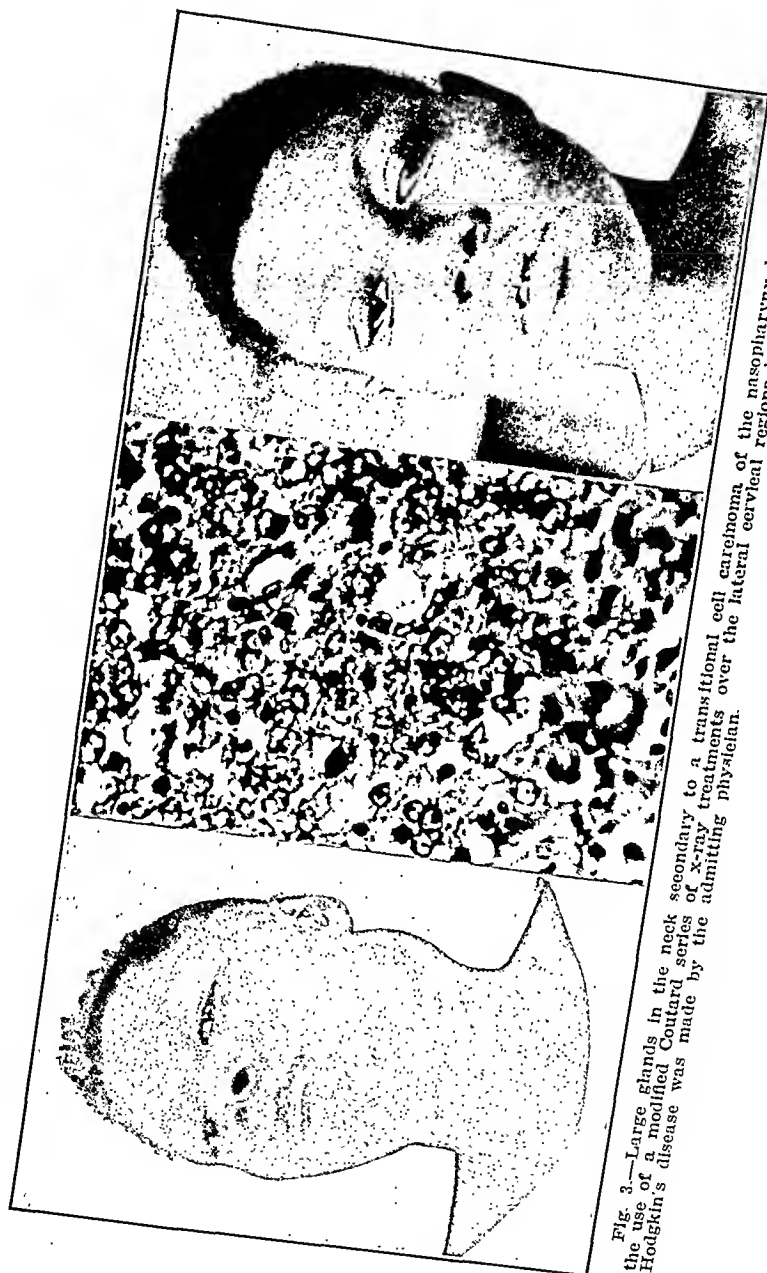


Fig. 3.—Large glands in the neck secondary to a transitional cell carcinoma of the nasopharynx before and after the use of a modified Coutard series of x-ray treatments over the lateral cervical regions in Case 3. A diagnosis of Hodgkin's disease was made by the admitting physician.

were: 220 kv., 20.0 ma., a target skin distance of 50.0 cm., and a filter of 0.8 mm. of tin, 0.25 mm. of copper, and 1.0 mm. of aluminum. By the time the series was completed the neck had a normal appearance and the nasopharynx was almost clear of disease.

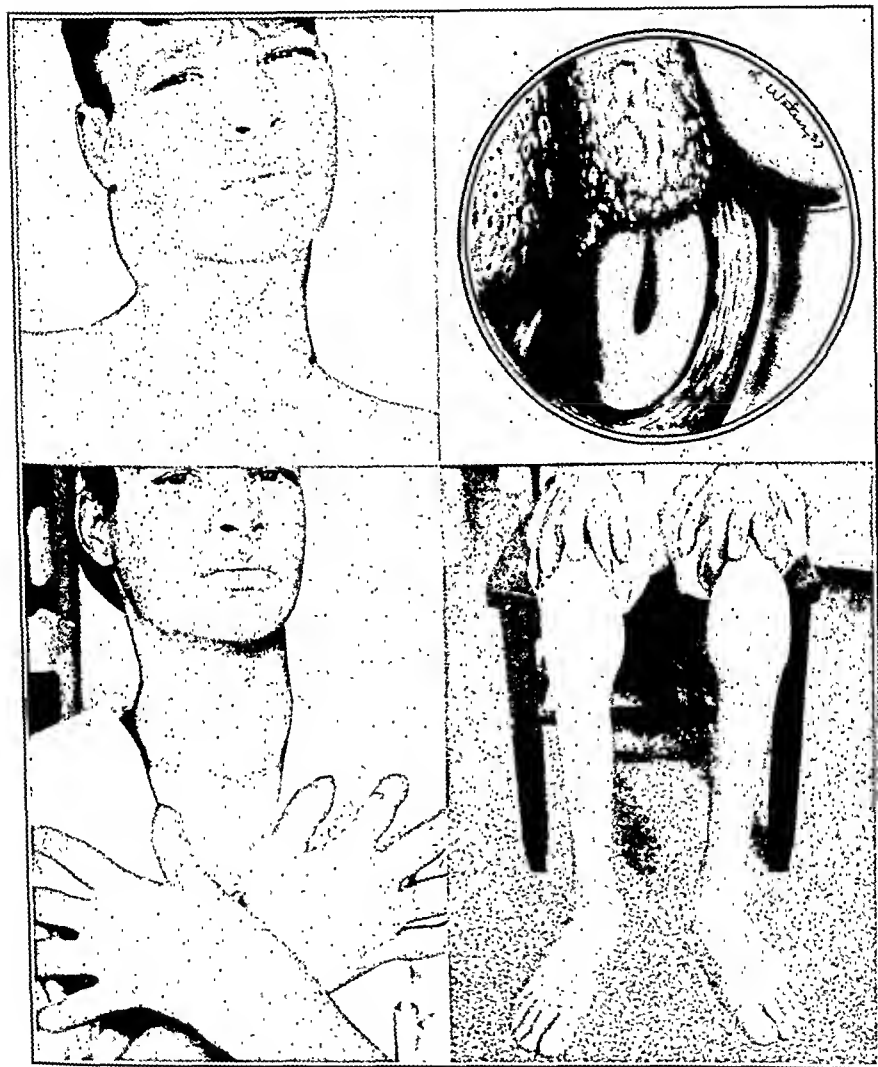


Fig. 4.—Transitional cell carcinoma arising in the right fossa of Rosenmüller and producing cervical adenopathy. The drawing represents the primary lesion as it appeared in the pharyngeal mirror. (This drawing is inverted.) The lower photographs show the pulmonary osteoarthropathy observed in the hands, knees, lower legs, and feet when he returned 6 months after x-ray treatment with no demonstrable evidence of malignancy present.

He returned five months later because of loss of weight, pain in the lower back, and loss of the control of his legs and bladder. A film of the chest revealed mediastinal nodes. His neck and throat still had a normal appearance. His hands and feet showed a generalized soft swelling and the fingers and toes showed a tendency toward clubbing. The knees were also swollen.

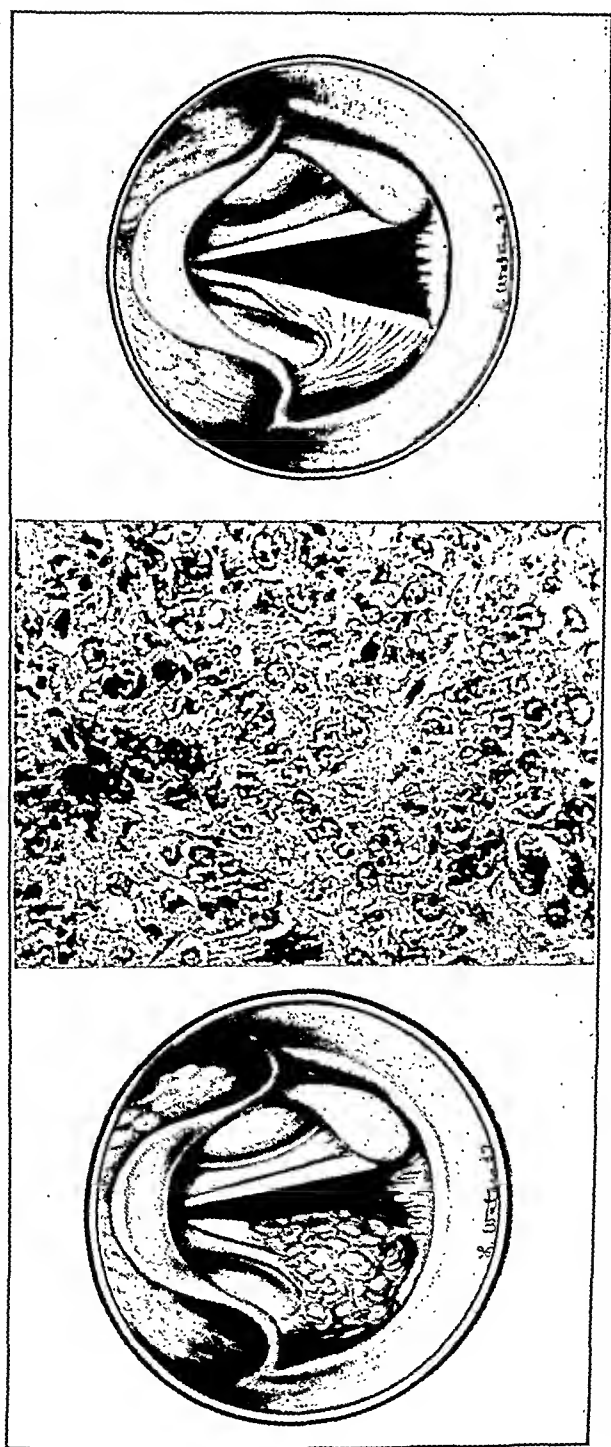


Fig. 5.—Drawings made from sketches of the laryngeal mirror appearances of an epidermoid carcinoma of the left vocal cord before and one year after treatment with a modified Coutard series of x-ray treatments in Case 5. The sketches were made by Dr. Lyle Sellars. The high power photomicrograph indicates the malignant nature of the tumor cells.

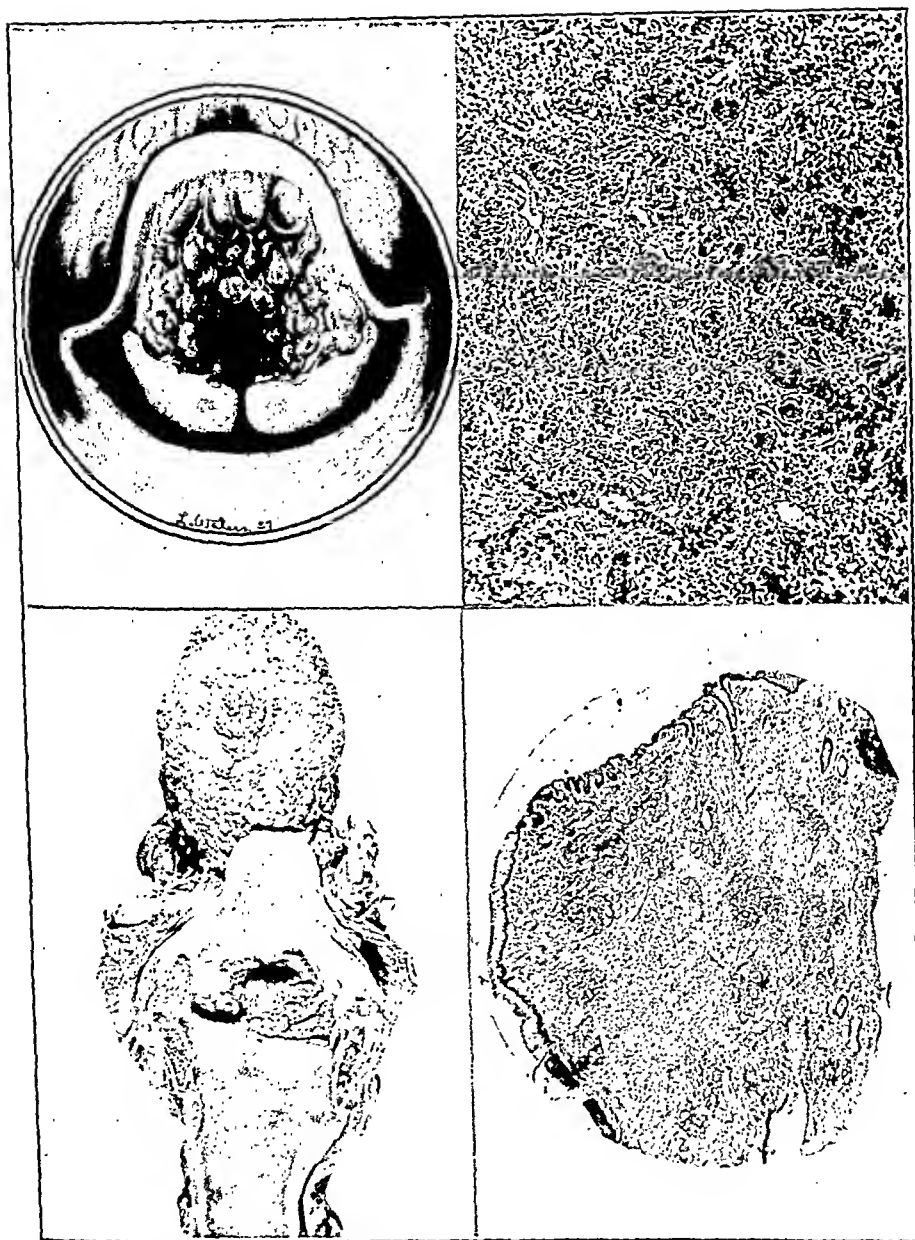


Fig. 6.—The drawing represents the laryngeal mirror appearance of a large adenocarcinoma of the larynx in Case 6. It was producing almost complete obstruction before x-ray treatment was administered. The upper photomicrograph is made from a biopsy specimen from this tumor. The photograph shows a shallow ulcer in the larynx as it appeared at autopsy 6 weeks after treatment, following death from a complicating lung abscess. The lower photomicrograph represents one of numerous sections showing no malignancy, taken from the edges of the residual ulcer. These illustrations prove that even a large carcinoma of the larynx may be eradicated with x-ray therapy.

Single erythema doses given over the entire spine produced some temporary relief, but he returned home where he died about two months later.

CASE 4.—A white boy, fifteen years of age, came to Baylor Hospital because of large painful glands in his neck and a rapid loss of twenty-five pounds in weight. His trouble started seven months previous to admission with a tinnitus on the right side. Glands soon appeared on the right side of the neck and grew rapidly so that they produced stiffness and soreness. After four months similar glands appeared on the left side of the neck.

Examination showed the patient to be a slender, poorly nourished boy who was very uncomfortable because of a hard tumor mass about 3 inches in diameter felt below the angle of the right jaw. Smaller nodes were felt on the left side in the same region. An examination of the throat done by Dr. Lyle Sellars revealed a tumor in the fossa of Rosenmüller on the right side just above the eustachian tube orifice. One of the glands was removed and the histologic diagnosis made by Dr. George Cald-



Fig. 7.—The photograph on the left represents the neck of a patient with an advanced, inoperable carcinoma of the larynx as it appeared one year after a series of modified Coutard x-ray treatments. There is still some carcinoma present but no tracheotomy tube is necessary. The other photograph represents the extensive metastases in the neck 2 months after a laryngectomy in an inoperable case. It seems evident that irradiation offers the best palpation in such cases.

well was transitional cell carcinoma, grade II. Doses of 3,300 r. to the right side and 2,700 r. to the left side of the neck were given through square portals measuring 15 cm. on a side. The factors used were 220 kv., 20 ma., a target skin distance of 50 cm., and a filter of 0.8 mm. of tin, 0.25 mm. of copper, and 1.0 mm. of aluminum. This treatment was given during a period of twenty-six days, and at the end of the series all evidence of the disease had disappeared both in the throat and in the neck.

He returned to the hospital after six months complaining of pain and swelling in his hands, feet, and knees. The fingers and the toes showed definite clubbing, but no evidence of pulmonary or cardiac disease could be made out. Roentgen ray examinations of the extremities showed periosteal changes in all of the bones examined of the type seen with pulmonary osteoarthropathy. Since similar clinical findings occurred in Case 3, carcinoma of the pharynx may be one of the underlying causes of

pulmonary osteoarthropathy. There was still no evidence of malignancy made out in the throat, neck, or chest at this visit.

CASE 5.—A white man, sixty-five years of age, came to the hospital because of a complete loss of his voice and some pain in the region of the right ear. He began to be quite hoarse four months before admission and the condition slowly grew worse until he could only speak in a whisper. Dr. McNelly made a diagnosis of carcinoma of the left vocal cord by inspection and Dr. Lyle Sellars removed a piece of tissue from this region. The biopsy report was epidermoid carcinoma, grade III. No external evidence of malignancy was palpable in the neck. Three hundred roentgens were given daily to alternate sides of the larynx, using circular ports measuring 7 cm. in diameter until each side received 3,000 r. The treatment factors were 220 kv., 20 ma., a filter of 2.0 mm. of copper and 1.0 mm. of aluminum, and a target skin distance of 50 cm.

When he returned six weeks after the series was finished, he had a fairly good, rather husky speaking voice and the vocal cords had a normal appearance except for the presence of a little edema.

One year and one month have elapsed since he was treated and Dr. Sellars states that the cords now have a normal appearance. He has a good speaking voice which is slightly husky, and he looks and feels quite well.

CASE 6.—A white man, fifty-six years of age, came to the hospital because of extreme dyspnea, loss of weight, and difficulty in swallowing. He had complained of cough and hoarseness for seven years, and six months before admission a piece of tissue diagnosed as carcinoma was removed from the intrinsic larynx in another institution by Dr. Lyle Sellars.

He stated that he had received thirty-four x-ray treatments over the neck in another laboratory, but his condition seemed to grow steadily worse so that breathing became very laborious and he developed a marked dysphagia causing him to lose a total of sixty pounds.

At admission Dr. Sellars reported the intrinsic larynx completely filled with carcinoma, except for a slitlike opening in its central portion. No glands were felt in the neck. A piece of tissue removed from the tumor was diagnosed by Dr. George Caldwell as adenocarcinoma, grade II.

Doses of 300 r. were given daily to alternate sides of the neck through round ports measuring 7 cm. in diameter, until a total of 3,000 r. was administered to each side using 220 kv., a filter of 0.8 mm. of tin, 0.25 mm. of copper, and 1.0 mm. of aluminum, and a 50 cm. target skin distance.

He had a cough and some temperature elevation when the treatment was finished, but his cough, which was now productive, continued. Roentgenograms of his chest showed a large abscess in the left upper lobe. His general condition did not improve and he died six weeks after the completion of the series of treatments.

A postmortem examination showed a depressed area about three-fourths of an inch in diameter in the inner wall of the larynx at the site of origin of the carcinoma as well as a large abscess in the left upper lung. Sections taken from the edges of the involved region in the larynx showed no evidence of carcinoma, and it seems fair to assume that this patient was free of malignant disease at the time of his death.

#### SUMMARY

Evidence is presented to show that irradiation therapy is the method of choice in all malignant tumors of the pharynx and larynx. Certainly it should replace surgery in all borderline and inoperable cases.

Single erythema doses given over the entire spine produced some temporary relief, but he returned home where he died about two months later.

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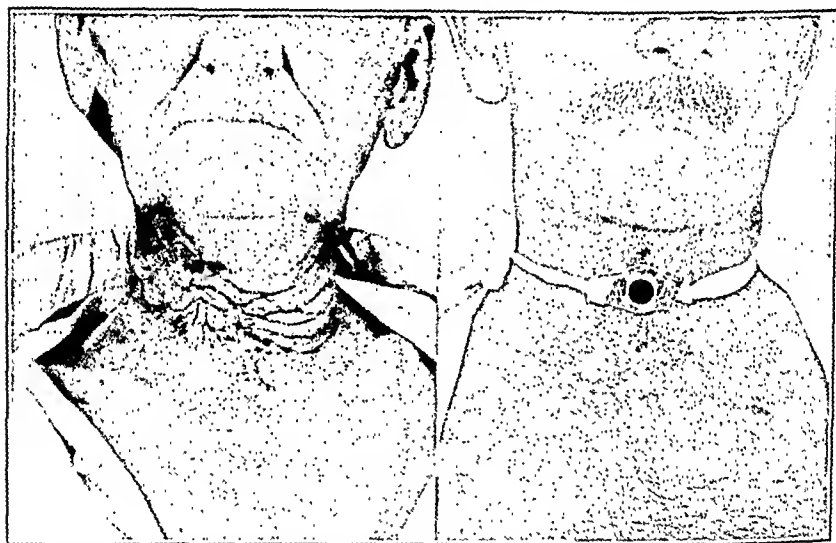


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# A STUDY OF THE LIPEMIA CURVE FOLLOWING SURGICAL OPERATIONS UNDER ETHER ANESTHESIA

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ON THE basis of their nontraumatic conception of the etiology of certain cases of fat embolism, Lehman and Moore,<sup>1</sup> in 1927, advanced the theory that certain ether deaths after prolonged anesthesia may be due to fat embolism and that a proportion of postoperative pulmonary complications might likewise be initiated by fat emboli in the lungs.<sup>2</sup> The results of their experimental work quite justified these speculations. They had actually produced pulmonary fat embolism by ether anesthesia in fat-fed dogs and demonstrated, by repeated chylomicron counts<sup>2, 3, 4</sup> during the course of anesthesia, a gradual diminution in the number of microscopic droplets in the plasma lipid emulsion. To explain these observations, the suggestion has been offered that ether may break the emulsion and dissolve free fat which then precipitates in alveolar capillaries as the ether vapor tension is reduced. This theory implies an actual reduction in the lipid content of the blood after ether anesthesia, which is contrary to the observations of all investigators in this field, who have employed quantitative chemical methods. An analysis of the work of these investigators, however, shows that in no case has the lipemia curve been followed after anesthesia into the period of recovery.

It is the purpose of this study to determine whether, in a small series of typical surgical operations under ether anesthesia, any characteristic lipemia curve or consistent lipid shift can be detected during the course of anesthesia or in the first twenty-four hours after operation.

## REVIEW OF THE LITERATURE

A. *Studies in Man*.—Only two investigators have reported quantitative chemical determinations of the blood lipoids before and after ether anesthesia in human subjects.

1. Potter<sup>5</sup> in "Changes in the Blood in Anesthesia," published in 1925, included determinations of the total fat, cholesterol, and total acid-soluble phosphorus upon oxalated whole blood of five relatively normal gynecological patients, taken one hour before and immediately

Received for publication, March 13, 1937.



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dogs. This difference was shown throughout the lipid partition with neutral fat 0.618 gm., or 266 per cent, higher; and lecithin 0.411 gm., or 313 per cent; cholesterol 0.167 gm., or 128 per cent; and free fatty acids 0.250 gm., or 284 per cent, higher than in the controls.

2. In 1914, Bloor<sup>8</sup> demonstrated a consistent but more modest rise (40 to 100 per cent) in the total blood fat content (fatty acids plus cholesterol, determined by the nephelometric method) of four dogs which had been subjected to ether anesthesia for from one to three hours, after variable preliminary starvation. While the lipemia curves were by no means identical, there was a decided rise, sharp at first, then gradual in three out of four, with an actual increase ranging from 0.12 per cent to 0.55 per cent and averaging 0.27 per cent total fat in the blood. Bloor suggested that this rise might be due to solvent action of the blood-ether mixture on fat depots in the tissues.

3. In 1916, Mann,<sup>9</sup> using Bloor's nephelometric method, determined the total cholesterol content of the blood in one 17.6 kg. bitch before and during prolonged ether anesthesia. The curve rose sharply from 0.266 per cent to 0.312 per cent during the excitement stage, and after one and one-half hours had dropped to 0.180 per cent. The peak, 0.358 per cent, was reached after seven hours of anesthesia.

4. In 1919, Duceeschi<sup>10</sup> subjected dogs to ether anesthesia for periods of sixty to ninety minutes daily and found a marked rise in blood cholesterol.

5. In 1931, Tetsu Kinoshita,<sup>11</sup> studying the effect of inhalation ether anesthesia upon the total fatty acids, cholesterol, and phosphatides of the blood of the rabbit, found that the fatty acids and cholesterol were increased, reaching a maximum three hours after narcosis, with a return to normal values after twenty-four hours. Phosphatides were decreased.

6. In 1933, Ghose<sup>12</sup> reported determinations (by Bloor's method of extraction and the Liebermann-Burchard reaction) of the cholesterol content of whole blood of 7 albino rabbits, before, during, and after drop ether anesthesia maintained for one hour and then forced to fatal termination. The values increased from an average normal level of 75.4 mg. per cent to an average of 92.5 mg. per cent during anesthesia and rose to a peak of 114.7 mg. per cent immediately after death.

7. Hospers,<sup>13</sup> also in 1933, determined total cholesterol (by Sackett's modification of Bloor's methods) in the whole blood of six rabbits and five dogs at thirty-minute intervals during open surgical ether anesthesia. In rabbits, the peak of cholesteremia was reached approximately one hour after induction of the anesthesia and varied from 38 mg. per cent to 100 mg. per cent above the normal level (60 to 90 mg. per cent), to which the curve gradually returned after four hours of anesthesia. In dogs, the hypercholesteremia was not as high and

after drop ether anesthesia induced by chloroform and lasting from fifteen to sixty minutes. There was identical fasting, catharsis, and preliminary medication (morphine gr.  $\frac{1}{4}$ , atropine sulphate gr.  $\frac{1}{50}$ ) in all cases. The phosphorus determinations were made by Zucker and Gutman's modification of Fitter's gravimetric method, but no mention was made of the methods employed for determining total fat or cholesterol. The total lipoid content increased in two cases (684 to 786 mg. per cent, 943 to 955 mg. per cent), decreased in two cases (933 to 798 mg. per cent, 1228 to 1219 mg. per cent), and remained practically unchanged in one case (918 to 920 mg. per cent). The cholesterol, determined in only three cases, showed very little change (225 to 227 mg. per cent, 216 to 210 mg. per cent, 239 to 221 mg. per cent). The total acid-soluble phosphorus increased slightly in four of the five cases (40.3 to 44.7 mg. per cent, 32.3 to 35.8 mg. per cent, 48.1 to 51.0 mg. per cent, 39.0 to 44.0 mg. per cent). In one case there was a decrease from 40.1 to 31.4 mg. per cent.

2. Mahler, in 1926, studying "Blood Cholesterol During Ether Anesthesia,"<sup>6</sup> made determinations of total cholesterol (free cholesterol and cholesterolin esters) by Lieboff's technique on the oxalated whole blood of two series (eighteen and thirty-seven cases) of unselected adults subjected to prolonged drop ether anesthesia induced by nitrous oxide. All patients were prepared by fasting for fourteen hours and by a hypodermic injection of morphia gr.  $\frac{1}{4}$  given thirty to sixty minutes before operation. Control determinations of cholesterol were made in every case immediately prior to induction of the anesthesia. No determinations of total fat or lecithin were made. The fasting control specimen in the combined series averaged 176.6 mg. per cent while the average of determinations made near the end of anesthesia (maximum in each case) was 209.6 per cent. There was a rise in every case and the average increase in total cholesterol content of the blood during ether anesthesia was 33.0 mg. per cent.

*B. Studies Upon Experimental Animals.*—Seven investigators have reported determinations of various blood lipoid constituents before and after ether anesthesia in dogs and rabbits.

1. In 1908, Reicher<sup>7</sup> paved the way for others by indicating that the blood fat content of etherized dogs was higher than that of unanesthetized control animals. Using gravimetric methods, he determined the fat, lecithin, cholesterol, and free fatty acids in an alcohol-ether extract of 100 c.c. of blood taken from each of two dogs subjected to ether anesthesia after preliminary fasting. Unfortunately, he did not make determinations before anesthesia on the same dogs, but comparison of the averaged determinations on the etherized pair with the average values obtained from a pair of control animals showed that the total blood fat content was 248 per cent higher in the anesthetized

thetia. The second specimen was taken as soon as surgical anesthesia had been obtained. The third was withdrawn at the end of operation while the patient was still on the operating table. The postoperative specimens were obtained at four-, eight-, and twenty-four-hour intervals. None of the patients were given food until after the twenty-

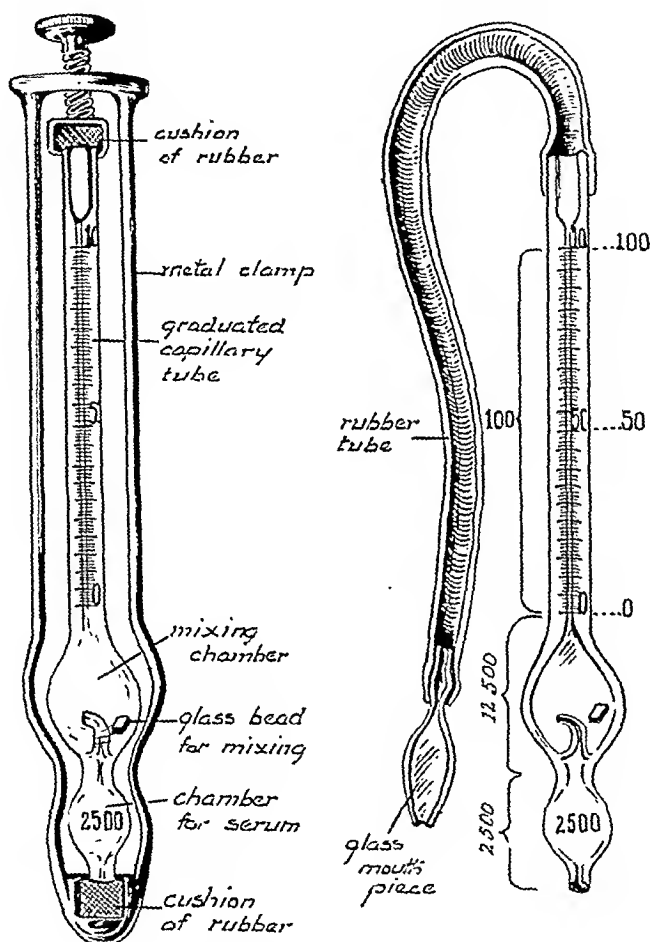


Fig. 1.—Rüchert's lipokrit pipette and clamp.

four-hour specimen had been taken, though a few received physiologic saline solution by hypodermoclysis or 10 per cent dextrose solution intravenously.

The total lipid content of the serum of each specimen was determined in duplicate by the lipokrit method.<sup>14</sup> This is a simple volumetric micromethod based on the principle of the Babcock test for milk fat. The lipoids are liberated from the serum in two fractions by the action of sulphuric acid, amyl alcohol, and centrifugation. The neutral fats, free fatty acids, and cholesterol break from emulsion

fluctuated more. The peak of increase varied between 18 mg. per cent and 42 mg. per cent, and the curve approached normal (130 to 150 mg. per cent) after five hours of anesthesia.

*It will be seen that all observers have reported an increase in the various blood lipid constituents during ether anesthesia except Potter, who was the only investigator to make determinations of total fat changes in man. While her series is small, the extreme variability of changes in total fat which she observed is more consistent with our findings than those of any of the other investigators.*

#### OUTLINE OF THE STUDY

It was obviously impossible to control the innumerable factors influencing lipemia in a heterogeneous group of diseased individuals subjected to various operative procedures and anesthetics. Prolonged preliminary starvation was out of the question and, furthermore, would have defeated the purpose of the study. Except in a few cases, there was no opportunity for determining the normal variation and probable error of the daily fasting blood lipid level in each individual before operation. It was, therefore, decided to accept as a standard the values for the early morning fasting total lipid content of the serum which we<sup>14</sup> had previously determined by using Rückert's lipokrit method<sup>15</sup> in a series of twenty-four normal adults on a regular hospital diet. This group was composed of twelve males and twelve females, ranging in age from eighteen to eighty-three years, with an average age of 34.7 years. None varied more than 10 per cent from the normal weight, for their height and age. Their fasting lipemia levels ranged from 427 ml. per cent to 703 ml. per cent, with a mean value of 550 ml. per cent. With these values as a standard fasting lipemia range, from which deviation could be measured, we proposed to use the same lipokrit method and plot the postoperative lipemia curves in twenty-four routine surgical patients.

The patients were not selected in any way except by the factor of their willingness to submit to repeated venipuncture and by our desire to obtain an equal number of patients given ether anesthesia and patients in whom some other anesthetic was to be used. One case was chosen at random from the operating schedule each day, without consideration of the nature of the operative procedure or the disease for which operation was to be performed. All patients fasted approximately fourteen hours before operation and received practically identical preliminary medication (morphia gr.  $\frac{1}{6}$  or  $\frac{1}{4}$ , and atropine gr.  $\frac{1}{150}$ ). A series of six specimens of blood were taken from each patient at significant intervals, before, during, and after operation, covering the twenty-four-hour period. The fasting or anteoperative specimen was drawn in the operating room just before induction of the anes-

normal fasting alimentary lipemia curves. The curves are well grouped within the normal fasting lipemia range (427 ml. per cent to 703 ml.

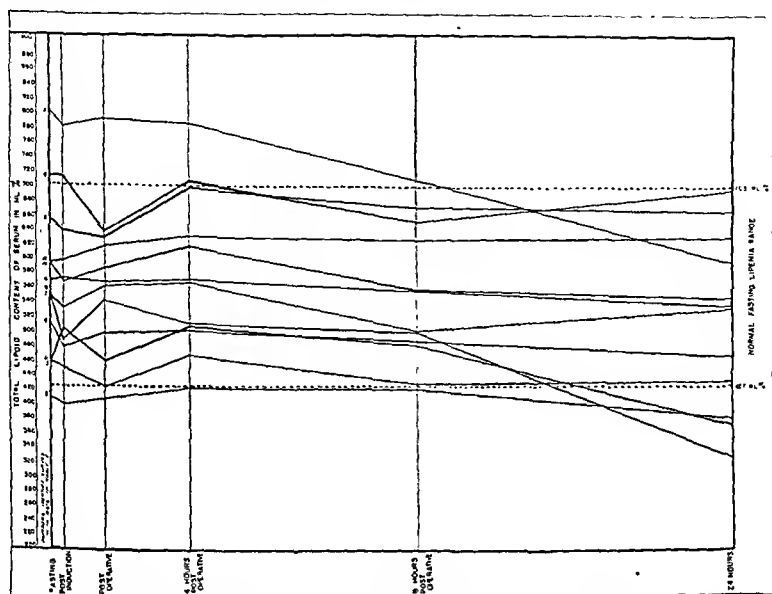


Fig. 2.—Lipemia curves of twelve patients operated upon under ether anesthesia.

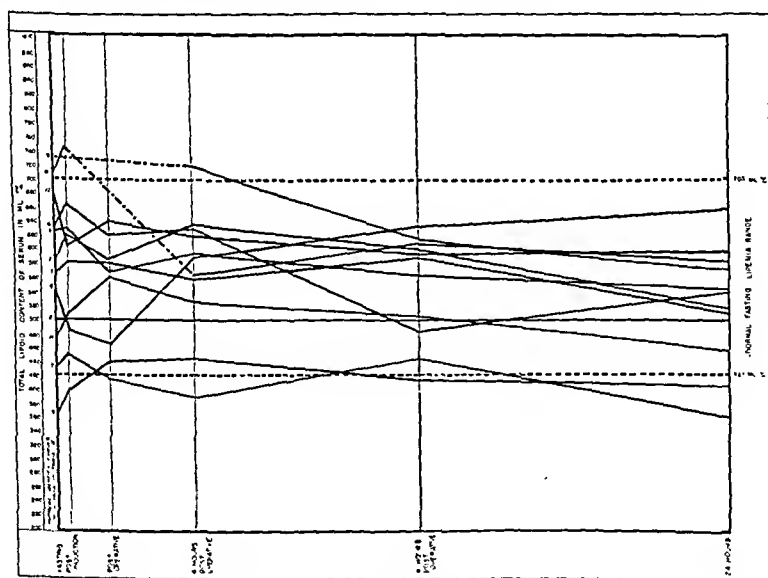


Fig. 3.—Lipemia curves of twelve control patients operated upon under anesthetics other than ether.

per cent), and again it is interesting to note that the only curves projecting above this range are those of the two patients who had been on a Sippy regime for several weeks.

almost immediately, while the fatty acids of conjugated lipides such as lecithin agglomerate after twelve hours of hydrolysis. This process is accomplished by means of Rückert's lipokrit pipette equipped with bulbs, in which the serum sample and reagents are automatically mixed in the proper proportions, and a calibrated stem in which the volume of coalesced lipid material may be measured after centrifugation (Fig. 1). The usual precautions were taken to render fat-free all needles, syringes, test tubes, and pipettes. After the blood had clotted, the serum was separated by slow centrifugation at 1,000 revolutions per minute and transferred to another tube by means of a capillary pipette. The lipokrit pipettes were then filled with serum and reagent mixture, shaken mechanically for five minutes, and centrifuged for ten minutes at 3,000 revolutions per minute. Whenever there was a discrepancy between the final duplicate values, the average of the pair was recorded.

In order to detect gross shifting of plasma fluid which might indicate mechanical dilution or concentration of the lipid emulsion, the cell volume of each specimen of blood was determined by Wintrobe's method.<sup>16</sup> Inasmuch as vacuum-dried heparin vials were used for collection of these samples, the usual correction for cell shrinkage due to sodium oxalate was omitted.

## RESULTS

In Table I, the lipokrit and hematocrit results are tabulated for each of the twelve ether anesthesia patients. The sex, color, age, percentage over or under normal weight, diagnosis, operation, and quantity and duration of anesthesia are recorded for each patient. The patients are arranged in order of their deviation from normal weight, progressing from the thinnest to the most obese. It is interesting to note that the two highest fasting lipemia levels were found in thin peptic ulcer patients on Sippy diet. Correction of the lipokrit value for concentration or dilution according to the cell volume changes was found to indicate no significant alteration in total lipid content of the serum (that is, no change greater than 40 ml. per cent, which is the least significant reading of the lipokrit scale). A study of Fig. 2 will show that there is no characteristic pattern in this group of twelve post-operative lipemia curves. There is a tendency for the curves of the obese patients and one underweight patient with gallstones to rise in the first four hours after operation; but the rise could not be considered significant in any case. There is a tendency for all curves to fall at the eight-hour postoperative interval and most of them continue to drop throughout the twenty-four-hour period. The degree of fall, however, is in no case greater than we have already found in

TABLE II

LIPOKRIT AND HEMATOCRIT DETERMINATIONS IN THE LOCAL, SPINAL, NITROUS OXIDE, ETHYLENE, AND AVERTIN CASES

DATA PERTAINING TO PATIENTS COLOR, SEX, AGE, PER CENT OVER OR UNDER WEIGHT, DIAGNOSIS, OPERATION, ANESTHETIC, DOSE	TOTAL LIPOID CONTENT OF SERUM IN ML. PER CENT					
	CELL VOLUME IN PER CENT					
	F.	P.I.	P.O.	4 HR.	8 HR.	24 HR.
B., M., 57, wt. - 25%; secondary carcinoma of femur; thigh amputation; local, procaine, 1%.	585 37	625 37	590 36.5	640 35	605 32	520 30.5
W., M., 58, wt. - 13%; epigastric hernia; Mayo hernioplasty; local, procaine, 1%.	505 48.5	505 49.5	505 47.5	505 46.5	505 46.5	505 51
W., F., 53, wt. + 15%; umbilical hernia; Mayo hernioplasty; local, procaine, 1%.	570 31.5	585 32	585 32.5	575 33	495 31	515 31
B., M., 27, wt. + 17%; inguinal hernia; Ferguson hernioplasty; local, procaine, 1%.	365 47.5	400 49	445 48	450 47	420 49	410 52
W., M., 60, wt. - 20%; vesical calculus, cystitis; suprapubic cystotomy; spinal, 150 mg.	630 46	635 46	580 44	600 43.5	570 45.5	550 45.5
W., M., 57, wt. - 18%; hydrocele of tunica vaginalis; bottle operation; spinal, 150 mg.	635 46.4	670 48	625 47	635 47	490 45	545 46
B., M., 58, wt. - 10%; hypertrophy of prostate; bilateral vasectomy, cystotomy; spinal, 150 mg.	435 40.5	455 40.5	420 39	395 38.5	450 40.5	365 38
W., M., 63, wt. + 13%; gangrene of toes, diabetes; thigh amputation; spinal, 150 mg.	545 43	490 40	470 39	595 47	635 45	665 45.5
W., F., 41, wt. + 69%; cystocele, prolapse of uterus; Watkins' interposition operation; nitrous oxide.	735 46	* 46	* 42.5	725 42.5	625 41	575 39.5
B., F., 74, wt. - ?; gangrene of foot, arterial sclerotic; thigh amputation; nitrous oxide.	710 38	750 37	* 36	570 31.5	615 34.5	590 38.5
W., M., 27, wt. - 5%; acute appendicitis; appendectomy; ethylenc.	475 47	510 46	565 48.5	530 49	510 50	460 46
W., M., 61, wt. - 18%; inguinal hernia, recurrent; hernioplasty with Gallie suture; avertin.	685 46.5	610 46	645 46.5	625 45.5	600 45.5	605 44.5

ularly prior to administration of the spinocaine. The only curve which projects above the normal fasting lipemia range was that of an extremely obese patient who was subjected to a Watkins interposition operation under nitrous oxide anesthesia. Unfortunately, some of the values for the lipokrit determinations in the nitrous oxide anesthesia cases are not available because of breakage during centrifugation. Considered as a whole, however, this group of control postoperative lipemia curves is well within the limits of the accepted normal fasting lipemia range.

## SUMMARY

1. This study of the twenty-four-hour lipemia curve of twelve patients subjected to various surgical operations under ether anesthesia



TABLE I

LIPOKRIT AND HEMATOCRIT DETERMINATIONS IN THE 12 ETHER ANESTHESIA CASES

DATA PERTAINING TO PATIENTS COLOR, SEX, AGE, PER CENT OVER OR UNDER WEIGHT, DIAGNOSIS, OPERATION, DURATION, ANESTHETIC, DOSE	TOTAL LIPOID CONTENT OF SERUM IN ML. PER CENT CELL VOLUME IN PER CENT					
	F.*	P.I.*	P.O.*	4 HR.	8 HR.	24 HR.
W., M., 36, wt. - 25%; ulcer obstructing pylorus; posterior gastrojejunostomy, 1 hr.; ether 600 ml.	805 44	785 44	795 47	790 44.5	715 44.5	600 39
W., F., 40, wt. - 18%; cystic duct calculus-hydrops; cholecystectomy, choledochotomy, 2 hr.; ether 650 ml.	655 45	640 45	630 46	700 48	675 47	670 46
B., F., 31, wt. - 10%; chronic salpingitis; salpingo-oophorectomy, right, 1 hr.; ether 540 ml.	460 40.5	450 39	425 38.5	470 40.5	430 39.5	435 39.5
W., M., 39, wt. - 10%; duodenal ulcer; Finney pyloroplasty, 1½ hr.; ether 600 ml.	715 49	715 48	640 48.5	710 51	655 49.5	700 47
B., F., 23, wt. - N.; retroversion of uterus; Gilliam suspension, appendectomy, ½ hr.; ether 150 ml.	410 49	400 48	410 47.5	425 50.5	425 49	385 49.5
B., M., 23, wt. - N.; bullet wound femoral artery; amputation gangrenous leg; ½ hr.; ether 90 ml.	570 19	575 19.5	570 19.5	575 19	560 17.5	540 19.5
B., M., 39, wt. + .5%; radial N. injury—fracture; neurolysis, open reduction, 2 hr.; ether 400 ml.	550 38	535 38	565 40	570 40	505 36.5	535 37
B., F., 23, wt. + 10%; chronic salpingitis; bilateral salpingectomy, 1 hr.; ether 200 ml.	560 40	490 38	545 38.5	515 41.5	505 40	330 42.5
B., F., 42, wt. + 15%; fibromyomata of uterus; panhysterectomy, 1½ hr.; ether 315 ml.	515 26.5	480 27.5	500 28	505 28.5	490 29	470 29
W., F., 49, wt. + 20%; cystocele, rectocele; perineorrhaphy, Gilliam suspension, 1½ hr.; ether 375 ml.	595 50.5	570 49.5	590 49.5	620 49.5	560 49	550 50
W., F., 49, wt. + 40%; chronic cholecystitis; cholecystectomy (calculi), 1 hr.; ether 600 ml.	455 49.5	505 49.5	460 50	510 52	485 49.5	375 50
W., F., 60, wt. + 80%; carcinoma of body of uterus; panhysterectomy, 1¼ hr.; ether 375 ml.	595 46	600 47.5	620 47	635 46	630 46	635 48

\*In Tables I and II the abbreviations F., P.I., and P.O. are used as follows: F. denotes that the specimen of blood was taken after 12 hours fasting; P.I. denotes that the blood specimen was taken immediately before the induction of the anesthesia; and P.O. denotes that the blood sample was taken at the close of the operation.

Table II gives the data for the twelve control patients subjected to operation under other forms of anesthesia. It will be seen that four patients received local procaine anesthesia; four were given spinal anesthesia; two received nitrous oxide inhalation anesthesia; and of the remaining two, one received ethylene and the other was given tribromethanol by rectum. Fig. 3 shows that there is even greater variation in the pattern of the lipemia curves of these control patients. It is interesting to note that in three of the four patients operated upon under spinal anesthesia the lipemia curve rose abruptly after injection of the spinoecaine. However, this rise may have been an effect of ephedrine (3 c.c. of 3 per cent solution) injected intramus-

## THE DIAGNOSIS AND SURGICAL TREATMENT OF PERFORATING LESIONS OF THE COLON\*

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### GENERAL CONSIDERATIONS

IT IS useful and proper to regard those lesions of the large intestine with which the idea of "tumor" is in any way associated as being of neoplastic or of nonneoplastic nature. The neoplastic lesions are the true blastomas, tumors in the more specific and apparently more widely accepted use of the word. The nonneoplastic tumefactions are inflammatory processes, resulting from infection by microorganisms, to the presence of which the reactive submucosal and serosal intestinal tissues respond in a highly productive manner, giving origin to the idea of tumor, but in its broader and strictly etymological sense. The inflammatory tumefactions are known also as infectious granulomas and pseudotumors of the intestine.

Analyzing these processes further, the neoplastic lesions may be subdivided according to histologic type, the nonneoplastic tumefactions on the basis of etiology and pathogenesis, as in Table I.

What some may consider to be a somewhat unconventional way of regarding these intestinal tumefactions is to be assumed if the term perforating lesions is to be applied to them. The nonneoplastic tumefactive lesions are, without exception, infectious processes. The microorganisms causing them gain access to the submucosal and serosal intestinal tissues most frequently by penetrating the mucosal surface, which is accomplished the more easily, of course, if that surface has been damaged by disease or trauma. Less relevant to this part of our discussion are the other possible avenues of infection, namely, through the serosal surface by extension from a contiguous inflammatory lesion, and embolically, from a more remote focus. Thus the nonneoplastic tumefactive lesions are considered to be essentially perforative in character, the neoplastic only potentially so. Almost any neoplasm projecting into the intestinal lumen is an infected lesion. If it is an infiltrating process, as the malignant neoplasms are, the infection is carried to the deep tissues with advancing neoplastic growth. Infection of the submucosal tissues occurs also as a result of the trauma to which neoplasms, both benign and malignant, as well as the mucous membrane immediately adjacent to them, are notoriously subject. It

\*Read before the meeting of the Western Surgical Association, Kansas City, Missouri, December 11 and 12, 1936.

Received for publication, February 24, 1937.

shows no typical curve pattern or tendency when compared with the curves obtained in twelve patients operated upon under other forms of anesthesia.

2. In none of the twenty-four patients studied did the lipemia curve project significantly beyond an arbitrary normal fasting lipemia range.

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produces increased intraluminal pressures, sufficient in many instances to break or split the indurated neoplastic tissue which is rendered the more frangible the more infected it is.

Such is the origin and development of our conception of the perforating lesions, a term applicable to the purely inflammatory tumors on the one hand, and to the neoplastic lesions, when complicated by inflammation of sufficient degree to obscure their otherwise distinctive morphologic characteristics, on the other. From the standpoint of surgical management, the coexistence of this amount of inflammatory reaction with a neoplastic lesion not only confuses the diagnostic problem, at least until such time as a proper section of the diseased tissue can be submitted for microscopic examination, but it also imposes operative difficulties and hazards otherwise not encountered. The freedom with which the diseased segment of intestine can be handled, either as it is explored or as it is mobilized in the course of an operative procedure, is greatly limited, both because some degree of fixation is always to be found, and because injudicious manipulation certainly promotes spread of the already existing, but presumably localized, peritonitis.

#### THE ROENTGENOLOGIC DIAGNOSIS

The treatment and prognosis in tumefactive lesions of the large intestine are conditioned primarily on whether they are of neoplastic or of nonneoplastic nature. Since it has been found that roentgenologic methods can be made to be so very efficient in establishing this vitally important differentiation, this phase of the diagnosis is to receive, in the discussion that is to follow, a particular, but it is hoped not disproportionate, emphasis. The lesions of the rectum and lower sigmoid within reach of the proctoscope are left out of consideration here for the reason that no less direct diagnostic method could conceivably be more accurate and reliable than the competently performed proctoscopic examination is in the diagnosis of these lesions. The roentgenologic examination competently performed takes precedence over all other diagnostic methods applied to the colon for the same reasons, namely, that its diagnostic elements are such that they enable the examiner to reconstruct in his mind's eye the gross morphologic features of the lesions he exhibits, and to interpret them in terms of pathologic anatomy.

It may be affirmed that the roentgenologic examination can be made to reveal the presence of any tumefactive lesion of the large intestine, at least as early in its development as it is able to manifest itself by clinical signs and symptoms. Such lesions are exhibited roentgenologically by producing what is called a filling defect, which may be defined as a constant, persistent subtraction from the normal contour outlines. It is produced chiefly by protrusion of the tumefactive substance

TABLE I

## CLASSIFICATION OF TUMEFACTIVE LESIONS OF THE INTESTINE

*A. Neoplastic: the true blastomas*

## I. Malignant:

Carcinoma

Sarcoma

## II. Benign:

*A heterogenous histologic group including adenoma, lipoma, fibroma, myoma, hemangioma, and even chondroma and osteoma*

*B. Nonneoplastic: inflammatory tumefactions*

## I. Primary:

(1) Hyperplastic ileocolitis, typhlitis, and pericolicitis, the etiology of which is:

(a) Known: tuberculous, amebic, streptococcic, actinomycotic, rarely syphilitic, typhoidal

(b) Unknown: fibroplastic appendicitis, other inflammatory tumefactions

(2) Diverticulitis

## II. Secondary:

(1) To extension of inflammatory processes from adjacent or contiguous abdominal organs: gallbladder, ovaries and ovarian tubes, seminal vesicles, omentum, mesentery

(2) To segmental injury (foreign bodies, coproliths, circulatory disturbances)

is conceivable, then, that the same microorganisms which cause the inflammatory intestinal tumors may utilize the site of mucosal damage incident to neoplastic disease as a convenient portal of entry into the more reactive tissues of the intestinal wall, there to incite the development of a lesion of dual nature, having neoplastic as well as inflammatory components. Once instituted, the inflammatory process not infrequently succeeds in its tendency to overwhelm the original neoplastic lesion to such an extent that the fairly distinctive, gross morphologic features of the neoplastic lesion are altered to resemble, in almost every particular, the very much less readily appraised gross morphologic features of the purely inflammatory tumors. With this change in form and structure there is a corresponding change in clinical and roentgenologic manifestations, so that ultimately the entire syndrome is that of a nonneoplastic, rather than that of a neoplastic, lesion.

It seems not unreasonable to assume that any neoplastic lesion of the intestine will eventually be attended with perforative-inflammatory manifestations, provided only that it be permitted to go its own way for a sufficient length of time; and the higher the grade of malignancy the greater will be the tendency in this direction. Another factor certainly encouraging perforation is the obstruction incident to the presence of a neoplastic lesion. Whether due to gradual reduction in luminal caliber by increasing encroachment of the neoplastic substance, or to the tendency toward intermittent or persistent, partial or complete intussusception which all neoplasms seem to have in some degree, obstruction evokes increased peristaltic activity. This in turn

produces increased intraluminal pressures, sufficient in many instances to break or split the indurated neoplastic tissue which is rendered the more frangible the more infected it is.

Such is the origin and development of our conception of the perforating lesions, a term applicable to the purely inflammatory tumors on the one hand, and to the neoplastic lesions, when complicated by inflammation of sufficient degree to obscure their otherwise distinctive morphologic characteristics, on the other. From the standpoint of surgical management, the coexistence of this amount of inflammatory reaction with a neoplastic lesion not only confuses the diagnostic problem, at least until such time as a proper section of the diseased tissue can be submitted for microscopic examination, but it also imposes operative difficulties and hazards otherwise not encountered. The freedom with which the diseased segment of intestine can be handled, either as it is explored or as it is mobilized in the course of an operative procedure, is greatly limited, both because some degree of fixation is always to be found, and because injudicious manipulation certainly promotes spread of the already existing, but presumably localized, peritonitis.

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toward and into the lumen, partly by diminished distensibility of the infiltrated wall. It is a manifestation of diseased but living tissue, hence certain changes in appearance are to be expected as a result of a possible, not entirely interrupted, intestinal motility. The filling defect corresponds to the intraluminal contours of the lesion which is its cause, and the roentgenologic diagnosis is based upon such morphologic features of the filling defect as reflect the pathologic anatomy of the lesions capable of producing them.

Carcinoma of the large intestine is manifested roentgenologically by signs so consistently distinctive that they are considered to be only slightly less pathognomonic than the gross morphologic picture itself.

The typical neoplastic filling defect is always confined to a relatively short intestinal segment, and describes a more or less marked, but relatively pervious, narrowing of the lumen. The canal through the neoplastic substance may have smooth tubular contours. Its course may be straight or irregularly angular, but almost always it is somewhat eccentric to the normal intestinal lumen proximal and distal to it. A most significant feature is the abrupt demarcation between involved and uninvolved intestine (Fig. 1). A mucosal relief pathognomonic of neoplasm can be described; and this is the most fundamental, the most reliable, and the most generally applicable, although not the most easily elicited, of all the roentgenologic signs of neoplasm of the colon.

Different histologic and gross morphologic types of carcinoma present different intraluminal relief patterns, but the normal relief is always entirely obliterated. Often, especially with the annular or fibrosclerous carcinomas, the internal aspect of the involved segment is flat and roughly granular and there is a peculiar stiff rigid look about it. Other types of carcinoma exhibit this granular surface also, but associated with it is a disordered arrangement of irregular depressions and elevations, resulting in a gnarled, coarsely-jagged relief. Polypoid carcinoma produces a marginal filling defect only when ulcerated, in which case the relief pattern reflects its saucerlike form; but again the granular amorphous character of the surface is apparent, broken irregularly by elevations corresponding to the excrescences of carcinomatous substance on the surface. Invariably apparent, however, and the most telltale feature of the neoplastic relief pattern, is the abruptness with which it is delimited from the uninvolved mucosa proximally and distally contiguous to it (Fig. 2). An expression of this sharp delimitation is the seemingly persistent tendency of the unperforated, neoplastic lesion toward intussusception. This is manifested roentgenologically by the appearance of unilateral or bilateral crescentic spurs at the proximal or distal extremity of the channel, or both, at the time when the lesion and the adjacent intestine are well distended with contrast material. This crescentic shadow complex is interpreted as an effort of the lesion to insert itself into the lumen of the bowel,

or as an attempt of the contiguous intestinal wall to fold itself around the tumor. Whatever the interpretation of this phenomenon is, only neoplastic lesions exhibit it, and it is a pathognomonic roentgenologic sign, particularly valuable when the channel is apparently or really impervious to injected or orally administered contrast material.



Fig. 1.—Typical filling defects produced by enema; *left*, ascending colon (opaque enema); *right*, descending colon (double contrast method).

The typical nonneoplastic filling defect is best defined as one in which the pathognomonic evidences of true neoplasm are lacking. It is essentially a constriction of the lumen, embracing only a part of one of the divisions of the large intestine, but it usually is a longer defect than the one associated with neoplasm (Fig. 3). The amount of constriction also varies within considerable limits. Some inflammatory tumors





FIG. 2.—The characteristic relief pattern of carcinoma: *left*, sigmoid colon; *right*, ascending colon.



Fig. 3.—Typical filling defects produced by nonneoplastic tumefactions (double contrast method): *left*, diverticulitis; *right*, tuberculoma. Both lesions are in the sigmoid colon.



Fig. 2.—The characteristic relief pattern of carcinoma: *left*, sigmoid colon; *right*, ascending colon.



FIG. 4.—Filling defects produced by perforating carcinoma with development of huge pericolic abscess: *left*, transverse; *right*, sigmoid colon.

narrow the lumen to such an extent as to render it entirely impervious, while others, of the same etiology, produce a narrowing which is hardly perceptible. Inflammatory disease in general is progressive and to a certain extent self-limited, and the gross morphologic as well as roentgenologic appearances depend largely on the stage of development at which the lesion is observed.

As has been indicated, neither the length of the filling defect nor the amount of constriction is constant, but all inflammatory tumors are alike in this respect that the filling defects they produce all fade off gradually, almost imperceptibly, into the normal contours of the intestine proximal and distal to the constricted area. Destruction of the mucosa may or may not take place, and when it is observed it is practically always in association with those inflammatory tumors caused by an etiologic agent which under other circumstances causes ulcerative colitis. The tuberculous, amebic, and the streptococcic granulomas are the principal examples of this group of inflammatory tumefactions. The most important pathologic changes are found in the submucosal structures; and while the mucosa has always undergone some pathologic change, it may be unbroken throughout the entire extent of the lesion. Combined involvement of ileum and cecum is commonly seen when an inflammatory tumor involves this region, a phenomenon never seen with neoplasm unless perforation has taken place. All of these morphologic features are reflected faithfully in the roentgenologic picture, but after all is said and done, the diagnosis of inflammatory tumor is made by eliminating the possibility of neoplasm as the underlying lesion.

When the roentgenologic examination has demonstrated that a tumefactive lesion is present, and has offered its dependable conclusions about the neoplastic or nonneoplastic nature of the tumor, it has made about as great a contribution to the final diagnosis as may be expected of it. There are no fundamentally reliable roentgenologic signs by which the various etiologic types of inflammatory tumor can be distinguished from each other, and the final roentgenologic diagnosis often, if not usually, reads "nonneoplastic tumefaction of indeterminate etiology." This noncommittal phrase is useful in that it does not bind the roentgenologic examiner to extend his diagnosis beyond the limitations of his method of investigation, although it is often possible, by keeping all the etiologic types of inflammatory tumefaction in mind and correlating these with a carefully elaborated clinical survey of the patient, to approximate the exact nature of a given lesion very closely.

The filling defect produced by neoplastic lesions which have perforated or which have otherwise been complicated by infection looks much more like the filling defect of the inflammatory tumors than like that of the true neoplasms (Fig. 4). As a result of the pericolic inflammatory process which is set up, the filling defect occupies a much

what has been said, be obvious. To do this, antispasmodic drugs, administered to full physiologic effect, are often useful in diminishing the increased irritability associated with these lesions. Often, too, roentgenologic examination after a short therapeutic regimen directed at alleviating the inflammatory component of the filling defect will permit the establishment of a diagnosis, otherwise of necessity left indeterminate. It may be said that a dependable roentgenologic diagnosis of neoplasm with perforation can be made whenever it occurs, and to confuse the condition consistently with the nonneoplastic tumefactions is to fail to exact the full diagnostic yield of the roentgenologic examination.

#### SURGICAL CONSIDERATIONS

We have given such lengthy and detailed consideration to the roentgenologic phase of the diagnosis, not in any sense to detract from the value of carefully and competently performed nonroentgenologic diagnostic maneuvers, but to emphasize the value of the roentgenologic method, to point out its work and its limitations, and to show why the classical roentgenologic signs of neoplasm fail when infection and neoplasm are intimately associated in the same lesion. Clinical signs and symptoms, although more indirect, may in certain instances be all but pathognomonic, but they are always of great value. Barger and one of us (Dixon) have described certain features of perforating neoplasm which have been of great diagnostic utility. One of these is the character of the reaction following the preoperative intravenous administration of a vaccine prepared from *Bacillus coli* and streptococci. The normal reaction, in the presence of nonperforating lesions of the colon, is an elevation of the temperature of the body from normal to 101 degrees to 103 degrees F. within ten to twelve hours. The temperature returns to normal abruptly and remains so after sixteen to seventy hours. If a perforating lesion is present, the reaction is characterized by a saw-tooth type of fever curve, the temperature of the body ranging from normal to 102 degrees F. for from three to six days. A similar reaction seems to be evoked by metastatic lesions in distant organs. To apply this test, of course, the existence of an intestinal neoplastic lesion must have been previously determined. It indicates inflammatory involvement of the peritoneum rather than the lesion which may have been its cause.

As indicated previously in this discussion, the coexistence of infection and neoplasm entails difficulties not encountered if the lesion is purely neoplastic or purely inflammatory. Whether complicated by infection or not, neoplastic lesions demand radical treatment, yet the very presence of infection may seriously impede the institution of the more radical surgical procedures indicated. The infections as well as the neoplastic component of the perforated neoplasm must be given serious consideration, and the surgical management, while aimed

longer segment of bowel than does the original lesion. The sharp demarcation between involved and uninvolved intestine disappears, and the filling defect tapers off gradually into normal external contours. Proximal and distal to the site of the original lesion, the mucosal pattern is markedly disturbed but not destroyed, and it is similar in almost all respects to that seen in association with inflammatory tumefactions. The tendency toward intussusception disappears. Diaeritical roentgenologic signs of the original lesion are not, however, obliterated beyond the point where roentgenologic methods fail to



Fig. 5.—Perforating carcinoma of the sigmoid colon; between brackets is the poorly demarcated filling defect; between arrows, the characteristic neoplastic relief pattern of carcinoma.

redeem them, and it is here that familiarity with the internal relief of the neoplastic lesion is of particular value. Situated often at or near the precise midpoint of the filling defect is an area manifesting a relief entirely different from that immediately proximal and distal to it, the pathognomonic internal relief of neoplasm, a frankly inadequate description of which was attempted above (Fig. 5).

The fundamental importance of obtaining adequate visualization of the entire extent of the filling defect, and of making a most careful study of the structural detail of its internal relief, should, in view of

firmed by other workers in Germany, France, and Japan. Many European surgeons have published reports indicating that the use of such antianaerobic serums has reduced the death rate from generalized peritonitis accompanying or following perforating appendicitis very appreciably. Our own observations lead to the belief that the death rate following removal of perforated lesions of the intestine has also been reduced as a result of the use of these serums. It is realized that evaluation of such experience is difficult, but vaccination has a logical appeal, and it appears that further use of the vaccine is recommendable since there is considerable evidence that the presence of certain anaerobic organisms creates a favorable environment for the growth of streptococci, *Escherichia coli*, and other aerobes which are commonly lethal in peritonitis. It seems probable that anaerobic organisms may be responsible for a greater number of fatal infections following resection of the colon than has heretofore been suspected.

Experience also indicates that the operative mortality can be reduced still more if some kind of short-circuiting operation is carried out before the diseased segment of intestine is resected. This encourages the subsidence of the concomitant inflammation, and this in turn facilitates the resection itself. Short-circuiting or sidetracking procedures are of particular advantage if the perforating lesion is situated well above the sigmoid colon. Ileocolostomy is done for lesions of the right half of the colon, and colocolostomy for those in the left half. As a rule such operations are not employable for lesions of the sigmoid or lower pelvic colon, because, if the greatest care is not exercised, contamination will occur when the lesion is subsequently removed. Preferably, the parietal peritoneum attached to the lesion is liberated and left as a patch over the lesion. This serves to prevent not only gross contamination, but also malignant implantation at the site of a possible "blowout." In cases in which this technic was employed, no attempt was made to approximate the peritoneum over the exposed muscle.

If feasible, perforating lesions of the colon are most satisfactorily managed by using a short-circuiting procedure as the first stage of the operation. If the lesion is in the pelvic colon or sigmoid, the portion of the parietal peritoneum involved in the inflammatory mass is to be freed with the lesion and used as a patch to prevent gross contamination. The use of anaerobic serum is recommended only because some of the fatal peritoneal infections following operations on the colon have, with apparent justification, been attributed to anaerobic microorganisms.

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directly at extirpation of the neoplastic process, is modified to minimize the added danger to the patient which the infectious component imposes.

The surgical treatment of diverticulitis provides an exemplification of these principles. In many instances this condition may be treated satisfactorily without surgical intervention. A combination of a low residue dietary regimen, methods of applying local heat, and antispasmodic drugs administered liberally often effects subsidence of the inflammatory process within reasonable limits of time.

The formation of pericolic abscess with and without extension to adjacent pelvic viscera, especially to the urinary bladder with the development of sigmoidovesical fistula, are among the more frequent complications of diverticulitis. Occasionally the pericolic abscess will drain spontaneously into the bowel and subside. If this fails to occur and the symptoms suggest that the abscess has become localized, institution of abdominal drainage is indicated. Fecal fistula may develop following such drainage and necessitate surgical treatment such as segmental resection. Spontaneous closure of the fistula may follow establishment of a temporary colonic stoma without direct attack on the fistula itself. After closure of the fistula, the continuity of the bowel can be reestablished.

Surgical treatment is usually necessary to bring about closure of a sigmoidovesical fistula. Here a temporary colonic stoma is made well above the fistulous opening in the bowel. Subsequently the involved segment of intestine is resected and the ends are brought together by end-to-end anastomosis. The opening into the urinary bladder is frequently circumscribed by so much induration that wide excision of that portion of the wall of the bladder is necessary. A suprapubic cystic stoma is usually established in these cases. The colonic stoma is closed later.

In the surgical treatment of intestinal tumefactions, it seems worthwhile to remark briefly about the use of intraperitoneal vaccine preoperatively. Accumulating experience seems to indicate that by this means the mortality from intestinal surgery is appreciably reduced. Intraperitoneal vaccination is therefore recommended. Some deaths from peritonitis still occur, of course, but in our experience their number has been strikingly lowered. If gross contamination occurs during an operation on the intestine, the insult to the peritoneum may be too great for it to overcome. In instances of contamination, anaerobic serum, as suggested by Weinberg, of the Pasteur Institute, for the treatment of peritonitis following perforation of the appendix, has been employed for the past two or more years. His studies showed that anaerobic microorganisms such as *Clostridium welchii*, *Bacteroides ramosus*, *Vibrio septicus*, and some others played important parts in the production of the peritonitis, and these findings have been con-

has resulted in much improved results. It was soon extended beyond the cases first seen in acute, complete obstruction and was employed in the treatment of partially and chronically obstructed tumor cases. A perhaps natural further extension was the idea advocated by some very able and experienced surgeons that all cases of tumor of the colon should be operated upon in stages, a preliminary colostomy being done routinely before excision of the growth is undertaken.

Now it is this last phase of the development of the divided attack that challenges criticism. Let it be remembered that the original purpose of the two-stage procedure was to limit the surgical interference to dealing with obstruction. What rational excuse can be advanced for applying this technique to a case that presents no obstruction? It would seem that this is another instance of the common human trait of following an established custom without analysis of why the custom was established. The discriminating position to take in regard to a first-stage colostomy would be to limit it to those cases of tumor in which obstruction actually requires it. Experience has shown that many cases of low-grade, partial obstruction may be quite satisfactorily operated upon in one stage by adequate preparatory treatment to clear up the partial obstruction, and certainly with no obstructive symptoms there is no need for a two-stage procedure.

But the scope of this discussion is more general than a consideration of colostomy in tumors of the colon. It should be remembered that there are clear and obvious objections to plural-stage operations per se. Each separate operation carries with it a separate hazard of hemorrhage, infection, potential complications relating to anesthesia, and the rare accidents like embolism. In addition, multiple-stage procedures nearly always mean increased hospital sojourn with added expense, loss of time, anxiety and delay in convalescence. These are weighty objections and must be offset by even greater benefits to justify the division of the surgical treatment into stages. In many cases such benefits do exist, and then it is wise to plan treatment accordingly. It is in no sense the intent of this article to oppose the principle of stage operations. As has been said, the idea is valuable and marks a step forward in practical handling of many difficult situations. The purpose of this article is, however, to insist that there is no inherent virtue in multiple-stage operations; that, on the contrary, there are definite and obvious disadvantages inherent in every divided operation and that each individual problem should be clearly analyzed before it is decided that a one-stage attack is unwise. In other words, the burden of proof always lies against the plural-stage operation.

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# Editorials

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## One-Stage or Plural-Stage Operations

A NOTEWORTHY advance has been achieved in many fields of surgery by the division of a surgical procedure into two or more separate operations. By this device the mortality of certain formidable situations has been definitely lowered, and other conditions that seemed too forbidding to justify surgical attack have yielded to such treatment with encouraging results. The principle has been widely applied in many diverse surgical domains. It may suffice to point out the highly toxic group of thyroid disease, various thoracic conditions, many plastic problems, and malignant disease of the alimentary tract.

It is perhaps inevitable that a method of demonstrated value should for a time, and by some surgeons, be utilized when it is not needed and where it is indeed unwise. The writer feels that something of the sort is happening now with the stage plan of operating and believes that a critical survey of the reasons for and against such a plan deserves a brief discussion. To choose a concrete example and a field with which the writer is most familiar, let us consider the case of malignant disease of the large bowel. Experience has demonstrated that direct attempts at removal of such tumors, when the patient is first seen while suffering with acute intestinal obstruction, are apt to result disastrously. The bowel above the obstruction is distended with highly toxic and infectious contents; its wall is edematous, with impaired circulation and often already invaded by bacteria; and the tissue is friable. Under such conditions, suturing or even excessive handling of the gut is fraught with great danger of peritonitis and general infection. In addition, the patient has all the constitutional disturbances that go with acute obstruction. It is not surprising that extensive resections in such a situation often turn out badly. Analysis of the disorder reveals the clear fact that the patient is suffering from two different although related conditions—acute intestinal obstruction and a tumor of the bowel—and that the former, an urgent emergency, has the right of way in treatment. The latter must wait for consideration until the emergency is past. It is obvious, therefore, that this clinical state calls for two divided surgical procedures: first, colostomy to relieve the obstruction; second, resection to remove the tumor; and separation of the first from the second operation by a period of time ample to permit complete recovery from the obstructive phase of the illness. The general acceptance of this division of the operative attack

These considerations lead to a conception of the rationale of sympathetic surgery which seems somewhat more logical than that involving an assumption of sympathetic disease. This conception may be simply expressed as follows: There is no known disease specific to the autonomic system; certain diseases, largely of fundamentally unexplained etiology, present sympathetic symptoms of importance in themselves; sympathectomy attempts to relieve these symptoms rather than to cure a disease. Such symptoms, of course, are illustrated by the Raynaud phenomenon, by the obstipation of megacolon, and by the elevated blood pressure of essential hypertension.

If this conception is preserved, three things will be accomplished. In the first place, a search for an underlying cause for unexplained disease will not cease. In the second place, we will save ourselves the embarrassing recollection of dogmatic statements that certain diseases have been cured, when in later years, after these diseases are better understood, we realize that relief of symptoms is all that has been effected. In the third place, we will tend to protect our patients from too extensive modifications of physiologic balance by sympathectomy for symptomatic relief alone.

The surgery of the sympathetic system, so far as present knowledge goes, must be thought of as being in the great majority of instances entirely symptomatic. When pathologic changes in the autonomic system are uncovered in association with the so-called sympathetic syndromes, this position can be modified.

Lastly, in maintaining this point of view, one need not minimize the value of sympathetic intervention. Skillfully applied to the relief of symptoms severe enough to warrant intervention, on indications intelligently developed and after adequate study, surgical attack on the sympathetic system offers a new factor in the therapeutic armamentarium of great present importance and perhaps even greater promise. Only let us recognize that when we attack the sympathetic, we attack symptoms and, in the light of present knowledge, not disease itself.\*

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\*The ideas herein expressed have already been presented as a part of the chairman's address before the Surgical Section of the Southern Medical Association at its meeting in November, 1933.

## The Surgery of the Sympathetic System

THE traditional functions of operative surgery are, first, the adjustment of injured tissues to facilitate the processes of repair; second, drainage to make easier the body's struggle against invading bacteria; and, finally, the direct eradication of diseased structures. To these, modern surgical development has added a new conception: the indirect attack on disease by the surgical modification of physiologic balances. Current operations on the sympathetic nerves and ganglia furnish the outstanding example of such indirect attack.

It is easy to assume that the surgery of the sympathetic system is directed toward the cure of disease; i.e., that sympathetic imbalance is the essence of disease. This common assumption involves a conception for which there is no real evidence. The lesions of trauma, inflammation, and new growth, grossly and microscopically identified, may occur at single or multiple focal points in the autonomic system anywhere from the hypothalamic centers or higher to the most distant peripheral fibers, producing symptoms and signs resulting from paralysis or stimulation of autonomic functions. The therapy of these conditions is obviously in most instances the therapy of the underlying pathologic process. Except for such identifiable focal lesions, it is probably proper to say that there is no known pathology of the autonomic system. To speak of diseases of this system is, therefore, unwarranted.

If one reviews the mechanism of the vast majority of everyday symptoms, one realizes that almost all are produced by impulses passing over the autonomic pathways. Fever, chills, colic, vomiting, dysuria, constipation, diarrhea, sweating, hunger, thirst, palpitation of the heart, dyspnea, and many varieties of pain are all closely associated with autonomic activity. In the vast majority of instances we do not think of the autonomic nature of these manifestations. Our minds are directed rather to possible underlying causes such as pulmonary tuberculosis or intestinal obstruction. Today, it would be actually possible to cure the night sweats of tuberculosis by sympathetic denervation, and theoretically possible to abolish the colic of intestinal obstruction by parasympathetic neurectomy. Only when the etiology of the disease is obscure, are we led to focus our attention on the fact that symptoms are expressions of autonomic activity. This may be illustrated by a phase in the history of the treatment of exophthalmic goiter, when relief of the predominantly sympathetic symptoms by sympathectomy was proposed and in many instances carried out. It behooves us at least to raise the question whether our modern operations on the sympathetic nerves may not in the future prove to have an equally illogical basis.

## THE SYMPATHETIC NERVOUS SYSTEM

The rationale of the surgical procedures which attack the sympathetic nervous system is based upon an interruption of cardiosensory and motor pathways. This was originally suggested by Franeois Franek<sup>4</sup> and first clinically tested by Jonnesco.<sup>5</sup> The numerous and various procedures advocated following Jonnesco's operation clearly reveal their unsatisfactory results. In order to explain the inconsistent results and to understand better the rationale upon which this method of surgical attack is based, it is necessary to review the underlying anatomic and physiologic principles in the light of recent investigations.

The presence of typical somatic afferent fibers in the sympathetic cardiac nerves is now definitely established. The histologic characteristics of these fibers have been excellently described by Ranson and Billingsley<sup>6</sup> and Stöhr.<sup>7</sup> Heinbecker<sup>8</sup> has further corroborated this fact by utilizing the cathode ray oscillograph to demonstrate that their electrical conduction properties are similar to those of afferent fibers in the ordinary sensory nerve. Strictly speaking, these nerves are not a part of the autonomic nervous system at all, but they simply utilize the sympathetic pathways to the heart to transmit afferent impulses from the heart to the central connection.

The sensory nerve endings of the heart and aorta are similar to those found elsewhere and have been shown by Stöhr<sup>7</sup> to be present in the heart muscle, endocardium and epicardium, and in the adventitia of the coronary artery. The neurones to these sensory endings converge in the periarterial plexus of the coronary arteries, traverse the superficial and deep cardiac plexuses and course in the middle and inferior cardiac nerves which join the corresponding cervical ganglia of the sympathetic chain. As there are no white rami communicantes between the cervical sympathetic chain and the spinal cord, practically all of these outbound fibers must descend to the upper thoracic ganglia and finally reach their cells in the spinal ganglia by passing through the white rami communicantes into the central portions of the first thoracic and upper four or five intercostal nerves. Aside from the well-established cervical cardiac nerves, Brauecker<sup>9</sup> and Ionesco and Enachesco<sup>10</sup> have recently shown that there also exist thoracic cardiac nerves which run directly across the posterior mediastinum to the upper thoracic sympathetic ganglia; that is, the upper four or five thoracic sympathetic ganglia. All of the thoracic and cervical cardiac nerves carry somatic afferent fibers except the superior cardiac nerve, which Ranson and Billingsley<sup>6</sup> claim is a purely motor pathway. Thus, it can be readily observed that all of the sensory pathways from the heart converge on the upper four or five thoracic sympathetic ganglia (Fig. 1).

This concept of the cardiosensory pathways has been recently corroborated by experimental investigations. In 1930, Sutton and Lueth<sup>11</sup>

# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## THE SURGICAL TREATMENT OF CORONARY DISEASE

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IT IS indeed remarkable that although Heberden<sup>1</sup> published his original disquisition concerning cardiac pain due to coronary artery disease in 1786, this important disorder was not clearly recognized until relatively recently, when Herrick<sup>2</sup> made his first important contribution in 1912. That a disease of such vital significance and relatively frequent occurrence, particularly among physicians,<sup>3</sup> should be relegated to almost complete desuetude for over a century and a quarter is extraordinarily amazing. However, during the past quarter of a century intensive anatomic, physiologic, and experimental investigations have established a more elucidative comprehension of the fundamental background of the malady and a more rational therapeutic approach.

The treatment of coronary artery disease and cardiac pain is of particular interest to the surgeon, because of its historical importance in the development of surgery of the sympathetic nervous system. The first successful clinical application of sympathectomy was based upon the radioinactive speculations of Francois Franck,<sup>4</sup> in 1899, and performed by Jonnesco,<sup>5</sup> in 1916, in a case of angina pectoris. The successful result of this first operation stimulated universal interest and the procedure was quickly and widely adopted. The brilliance of this first successful result was soon dimmed by the many disappointing failures in the hands of other surgeons. As a consequence, various modifications were advocated and divergent theories proposed which only added to the already existing bewilderment and confusion. In the light of recent anatomic and physiologic advances, this was obviously due to inadequate knowledge and insufficient comprehension of the underlying fundamental principles.

The present status of the surgical treatment of coronary artery disease and cardiac pain involves a consideration of three main methods of attack: (1) the sympathetic nervous system; (2) the thyroid; and (3) the development of a collateral blood supply to the heart.

have more recently demonstrated that cardiac pain produced in this manner in the normal dog could be relieved only by resecting the stellate ganglion and the upper four thoracic ganglia bilaterally. Similarly, cardiac pain impulses could be completely interrupted by cutting the upper five pairs of thoracic posterior spinal roots. Aside from this concept of cardiosensory innervation, Leriche<sup>13</sup> insists that there also exists a sympathetic sensory innervation per se, which he terms "une sensibilité reflex," with the stellate ganglion as the center of reflex activity. He is of the opinion that impulses originating in the cardio-aortic plexus travel up these sympathetic fibers to the stellate ganglion, and in the manner of a reflex arc, effect coronary vasoconstriction through the centrifugal sympathetic motor pathways.

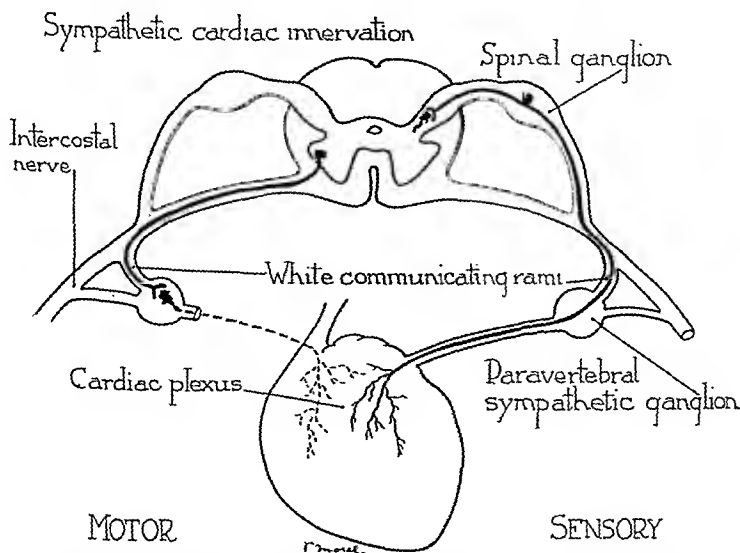


Fig. 2.—Diagrammatic representation of differences in motor and sensory cardiac innervation. On the left (motor cardiac innervation) the cell of preganglionic sympathetic fiber lies in the anterior lateral horn of the spinal cord and the neurone traverses the anterior root and the white communicating ramus to the paravertebral sympathetic ganglion where it synapses with the postganglionic cell, whose neurone courses to the cardiac plexus by way of the cardiac nerves. On the right (sensory cardiac innervation) the sensory fiber does not synapse in the sympathetic ganglion, but passes through it and the white communicating ramus to its cell in the posterior spinal root ganglion and connects with the spinal cord by way of the posterior root.

The vasomotor efferent or accelerator impulses to the heart and coronary arteries differ from the sensory in that they travel in the true sympathetic neurones (Fig. 2). As early as 1892, Langley<sup>14</sup> demonstrated that accelerator impulses leave the cord by the upper five thoracic pairs of anterior roots and their white communicating rami and assumed that their transmission occurred by efferent fibers which traveled upward in the sympathetic chain to synapse in the three cervical sympathetic ganglia and send their postganglionic neurones to the heart through the cervical cardiac nerves. After resection of both cervical sympathetic



published the results of their studies on the production of cardiac pain in dogs. They were able to produce the characteristic signs of pain in the normal dog by temporarily constricting the descending branch of the left coronary artery, and showed that these signs would rapidly disappear when the constriction was relieved. Utilizing a similar procedure to study experimental pain conduction, White, Atkins, and Garrey<sup>12</sup>

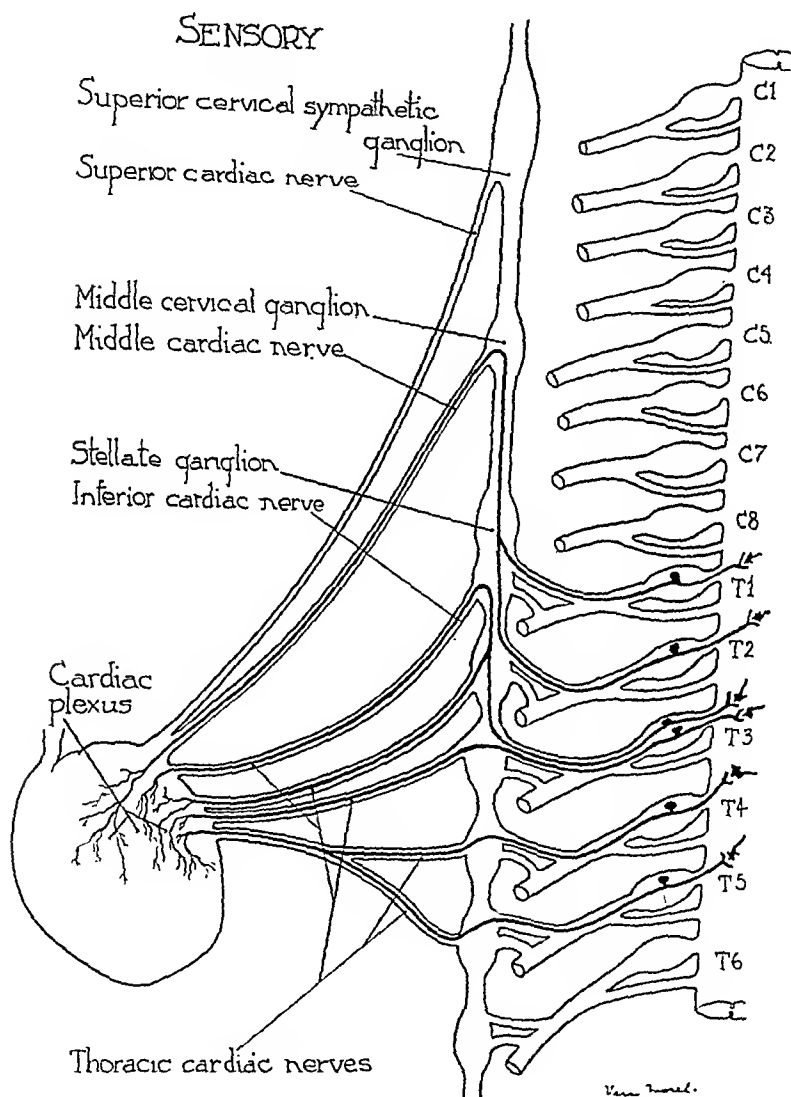


Fig. 1.—(Modified after Kuntz, Albert: *Autonomic Nervous System*, Philadelphia, Lea & Febiger, 1934, and White, J. C.: *The Autonomic Nervous System*, New York, The MacMillan Company, 1935.) Diagrammatic representation of the cardio-sensory pathways. These are true somatic afferent nerves, the ganglia of which lie in the posterior spinal root ganglia. No sensory fibers pass through the superior cervical sympathetic ganglion. Note that all sensory fibers from the heart pass through the upper five thoracic sympathetic ganglia and enter the cord through the corresponding posterior spinal roots.

levels. Higher ligation invariably produced death from ventricular fibrillation within a few hours. However, when both stellate ganglia had been previously excised, the animal usually survived and remained in good condition. Sympathectomy seemed to increase the collateral circulation. Similar results were obtained by Cox and Robertson.<sup>28</sup>

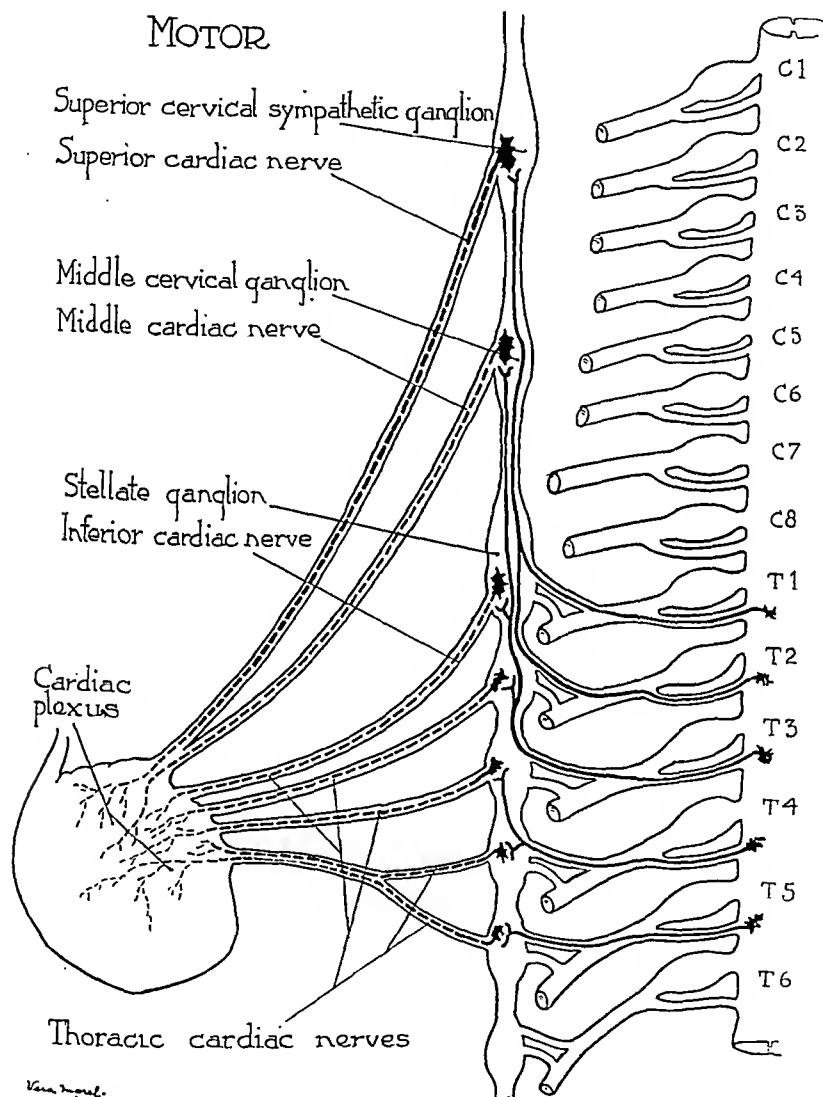


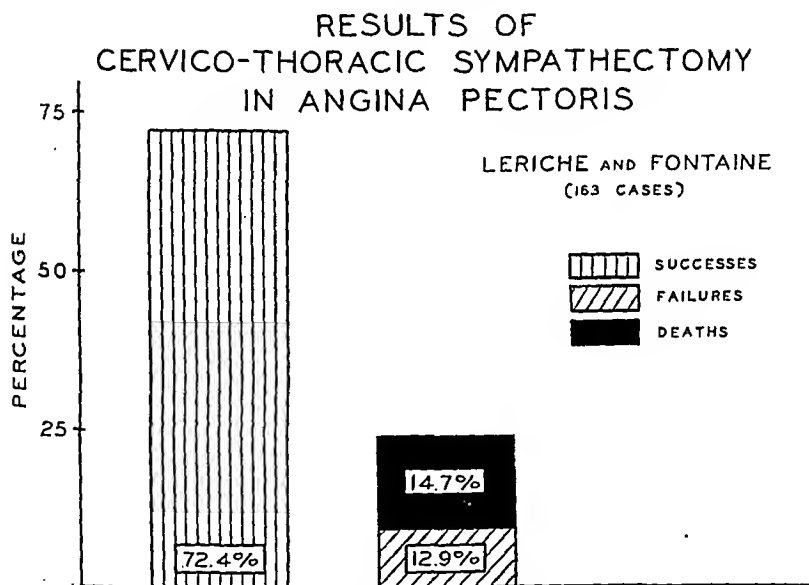
Fig. 3.—(Modified after Kuntz, Albert: *Autonomic Nervous System*, Philadelphia, Lea & Febiger, 1934; and White, J. C.: *Autonomic Nervous System*, New York, The MacMillan Company, 1935.) Diagrammatic representation of sympathetic motor innervation of heart. Presympathetic fibers course from their cells in the anterior lateral horn of the spinal cord from the first to the fifth thoracic segments through the corresponding anterior roots and the white communicating rami to reach the paravertebral sympathetic ganglia. Some make synaptic connections with the postganglionic cells in the upper four or five thoracic paravertebral ganglia; whereas, others course upward in the sympathetic chain to reach the inferior, middle, and superior cervical sympathetic ganglia. The postganglionic fibers communicate with the heart by way of the cervical and thoracic cardiac nerves.

chains, including the stellate ganglia, Cannon, Lewis, and Britton<sup>15</sup> observed that accelerator stimuli of nervous origin still reached the heart. White, Garrey, and Atkins<sup>12, 16</sup> found that faradic stimulation of the second and third thoracic ganglia after division of the sympathetic trunk above this level produced as much as a 58 per cent acceleration in the heart rate. The anatomic demonstration of the existence of the thoracic cardiac nerves which form direct connection between the upper four or five thoracic ganglia and the heart by Braueeker,<sup>9</sup> Ionesco and Enachescu,<sup>10</sup> and later by Kuntz and Morehouse,<sup>17</sup> explain these findings (Fig. 3).

Although there is considerable controversy as regards the nervous control of coronary circulation, at the present time the preponderance of experimental evidence indicates that vasoconstrictor fibers are carried chiefly in the vagus and vasodilators in the sympathetic nerves. As a result of his investigations, Greene<sup>18, 19</sup> came to the conclusion that the fibers which carry vasodilator impulses emerge from the first to the sixth thoracic segment of the spinal cord, and travel upward in the chain to synapse in the stellate, the middle cervical, and superior cervical sympathetic ganglia, although the greatest number travel through the stellate ganglion. Anrep and Segall<sup>20</sup> showed that in dogs stimulation of the vagi causes constriction of the coronary arteries and stimulation of the sympathetics produces dilatation. The interesting studies of Kountz, Pearson, and Koenig<sup>21</sup> reveal that in the normally beating heart vagus stimulation slows the rate and increases coronary flow; whereas, sympathetic stimulation accelerates the heart rate and reduces the coronary flow. This seems to indicate that the cardiac nerves act directly on the caliber of the coronary arteries and coincidentally have an indirect effect on the coronary flow through changes in the muscular activity of the heart. In their opinion, this latter mechanism is more important in regulating the blood flow in the wall of the normal human heart. Some of the more recent investigations suggest that the sympathetic nerves carry both constrictor and dilator fibers. The recent investigations of Greene<sup>22, 23</sup> particularly support this view. As the vagus trunk is known to derive sympathetic twigs from the superior cervical ganglion, it is possible that vasoconstrictor branches emerging from the thoracic sympathetic outflow and coursing upward to the cervical sympathetic chain to synapse in the superior cervical ganglion cross to the nodose ganglion and then pass down the vagosympathetic limb to the heart. However, this concept has not been completely confirmed.

Leriche and Fontaine<sup>24, 25</sup> and Leriche, Herrmann, and Fontaine,<sup>26, 27</sup> as a result of a series of extremely interesting investigations on the blood supply of the cardiac muscles, are of the opinion that the innervation of the coronaries follows the general law of vasomotor innervation; i.e., that coronary constriction is mediated by the sympathetics. They ligated the descending branch of the left coronary artery in the dog at different

attack has been upon the cervical sympathetic chain, including the stellate ganglion. Table I gives a summary of the results obtained by these various procedures as culled from the literature by different authors. Leriche and Fontaine's<sup>41, 42</sup> figures upon 172 patients selected from the literature and including their own are probably among the most representative. Of 163 cases in this group in which the results were known, 85, or 52.5 per cent, obtained good results; 33, or 20.2 per cent, showed some improvement; 21, or 12.9 per cent, showed failures; and 24, or 14.7 per cent, died. Thus, as is shown in Graph I, a little over 70 per cent will show some improvement to a greater or lesser extent. The probable explanations for these inconsistent results of cervical sympa-



Graph I.—Graphic representation of results of cervicothoracic sympathectomy in angina pectoris based upon 163 cases tabulated by Leriche and Fontaine.<sup>41, 42</sup>

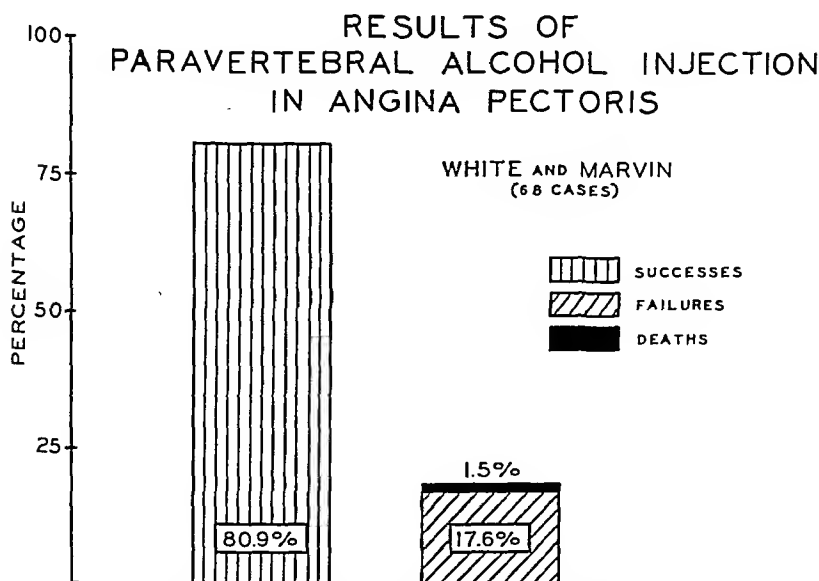
theetomy and the fact that better results are not obtained are that these procedures only partially interrupt the sensory pathways from the heart. In the light of the recent anatomical, clinical, and experimental investigations that have been discussed above, it becomes obvious that unless the accessory pathways through the thoracic cardiac nerves are interrupted, cervical sympathectomy alone is doomed to failure in a large number of instances. Thus, it is clear that the upper thoracic ganglia, the white communicating rami, and the posterior spinal routes are the focal points through which all cardiosensory impulses must pass, and any procedure designed to interrupt these sensory impulses should logically direct the attack towards these focal points; that is, the upper four or five thoracic ganglia.

White<sup>29</sup> believed this phenomenon to be not necessarily due to interruption of constrictor fibers of sympathetic origin, but rather to a paralysis of the cardiac accelerator nerves, which run through the stellate ganglia, with consequent alterations in muscle tone and diminished need for oxygen.

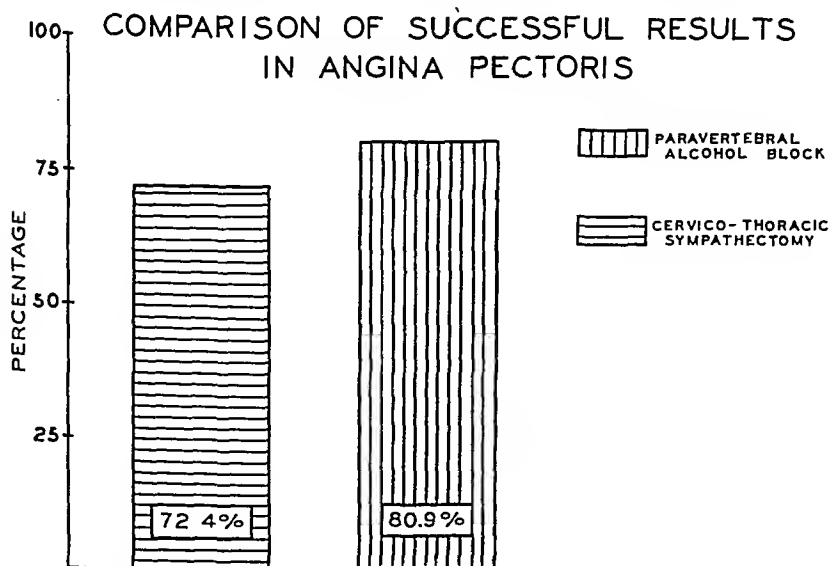
Most observers now believe that there is also present a tonic control of the coronary vessels, although the nature of this mechanism is still not very well understood. Some observers, such as Aurep, Hochrein, and Rein,<sup>30</sup> are of the opinion that this tonic constrictor action is maintained by fibers reaching the heart through the vagus nerves. On the other hand, Greene<sup>19, 22, 23</sup> and Hinrichsen and Ivy<sup>31</sup> are inclined to the view that the predominant dilator action is a function of the sympathetics passing through the stellate ganglion. A decision of this question is of more than academic importance, as has been emphasized by Danielopolu and his coworkers,<sup>32, 33</sup> because if the sympathetic dilators serve the important function of increasing coronary flow, then excision of the stellate ganglia for relief of angina pectoris is not only unjustifiable, but may in some instances even jeopardize the patient's life.

In 1916, Jonnesco<sup>5</sup> applied the procedure of sympathectomy for the first time in a case of angina pectoris. He removed the entire cervical sympathetic chain, including the stellate ganglion, bilaterally. Since then, a number of operations have been advocated on the cervical sympathetics, based upon divergent rationales with varying degrees of success. Coffey and Brown<sup>34</sup> advocated simplifying the procedure to extirpation of the superior cervical sympathetic ganglion, or cutting the cardiac branches of this ganglion. At the present time, Kerr<sup>35</sup> is one of the few surgeons who still advocates superior cervical ganglionectomy. In a recent publication, he reports complete relief of pain in 14 of 30 patients operated upon in this manner. The good results obtained by this procedure in these patients is difficult to explain in the light of recent anatomic and physiologic findings. Danielopolu<sup>36-38</sup> strongly condemns the removal of the stellate ganglion in any surgical procedure used in the treatment of angina pectoris, because the accelerator and dilator impulses pass through it. He suggests that the operation should consist of sectioning of the following nerves: cervical sympathetic chain, the vertebral nerve above the inferior cervical ganglion, the depressor nerve of Hofer, or any corresponding nerves present, and the nerve which springs from the cervical sympathetic chain above the superior cervical ganglion and passes to the heart. Although Leriche<sup>39, 40</sup> originally conformed to this view and performed section of cervical sympathetic chain above the stellate ganglion and ramisection of the stellate, more recently he<sup>25</sup> advocates stellate ganglionectomy. Other surgeons have either followed the procedures as advocated by the surgeons above or have modified the procedure slightly. However, in the main, the

considerably lower. Another advantage is the simplicity of performance, which of course makes it a procedure attended with little or no danger, particularly in these patients who are obviously such poor risks. However, a fair critical analysis of the procedure must not fail to



Graph II.—Graphic illustration of the results of paravertebral alcohol injection based upon 38 and 30 cases reported by White<sup>29</sup> and Marvin,<sup>40</sup> respectively.



Graph III.—Graphic representation of comparison of successful results obtained in the treatment of angina pectoris by cervicothoracic sympathectomy and paravertebral alcohol block. These results are based upon the cases reported by Lerlehe and Fontaine<sup>41</sup> for the former procedure and White<sup>29</sup> and Marvin<sup>40</sup> for the latter procedure.

Obviously, the ideal procedure should be resection of the upper four or five thoracic sympathetic ganglia. In this way all fibers carrying sensory impulses from the heart would be interrupted. However, such a procedure in patients who are admittedly poor risks would undoubt-

TABLE I

AUTHORS	NO. CASES	RESULTS: GOOD	IM- PROVED	FAIL- URES	UN- CERTAIN	MOR- TALITY
Reid and Andrus <sup>118</sup>	50	13	14	4	11	8
Cutler <sup>119</sup>	120	47	52	10	3	7
Fontaine <sup>41</sup>	94	59	11	6	5	13
Leriche and Fontaine <sup>42</sup>	78	26	22	15	4	11
Yater and Trewheila <sup>120</sup>	126	50	36	34	6	8
Orth <sup>121</sup>	98	52	14	9	4	19
Sarasola <sup>122</sup>	52	16	16	7		13

edly carry an unjustifiably high mortality. The method of Mandl,<sup>43, 44</sup> the paravertebral alcohol injection of the thoracic sympathetic ganglia, has been the solution of this difficulty. In this country, Swetlow<sup>45</sup> was the first to advocate paravertebral alcohol block for cardiac pain and to describe the technique in detail. He reported 8 cardiac patients suffering from attacks of severe precordial pain who were treated by paravertebral alcohol injections of the upper thoracic ganglia with prompt and satisfactory relief from pain in every instance. More recently, Mixter and White<sup>46</sup> and White<sup>47</sup> have perfected the technique and placed it upon a more rational basis. White<sup>29</sup> reports the results of paravertebral injections of alcohol for angina pectoris in 38 cases which have been followed over periods up to six years. These results are tabulated as follows: good (100 to 90 per cent relieved), 70.3 per cent; fair (90 per cent to 50 per cent relieved), 16.2 per cent; improved (50 per cent to 25 per cent relieved), 5.4 per cent; failure, 8.1 per cent; death, 1 case. The complications in this group consisted of troublesome intercostal neuritis, 3 cases; and recurrence of old bronchial asthma, 1 case. Levy and Moore<sup>48</sup> reported similar satisfactory results in 9 cases, and Marvin<sup>49</sup> in a more recent publication brought the cases of Levy up to 30. He stated that almost complete relief was obtained in approximately 40 per cent. A lesser degree of improvement was noted in another 30 per cent, and in the remaining 30 per cent the procedure was classified as a failure. Graph II illustrates the results of paravertebral alcohol injection in angina pectoris in the 68 cases reported by White and Marvin. It will be observed that successful results were obtained in 80.9 per cent of this group, failure in 17.6 per cent, and fatalities in 1.5 per cent. A comparison of these results with those of cervical thoracic sympathectomy is clearly illustrated in Graph III, and emphasizes more strongly the advantages of the former procedure. There is a higher percentage of successful results, and the mortality is

injection. These are made from  $3\frac{1}{2}$  to 4 cm. lateral to the spinous processes. This is approximately 2 to  $2\frac{1}{2}$  fingerbreadths (Fig. 4B). The points so marked lie opposite the seventh cervical and the upper three thoracic spines. Needles 8 to 10 cm. in length are then inserted at these points perpendicular to the surface of the back and at a depth varying from 3 to  $3\frac{1}{2}$  cm. to touch the upper four transverse processes. The needles are then inclined slightly in a caudal direction so as to slip beneath the transverse process or the angle of the rib and directed medially about 20 degrees towards the midline, and inserted for about 3 cm. or approximately 2 fingerbreadths (Fig. 4C). At this depth bone is usually touched, indicating that the needle is in contact with the lateral aspect of the body of the vertebra. At this stage, aspiration should always be done in order to determine whether the needles lie in a blood vessel or the subarachnoid space. Obviously if blood or spinal fluid is aspirated, then the position of the needle must be changed. When the needles have been placed in the correct position, 2 c.c. of 2 per cent novocaine adrenalin solution should be injected through each. Within a period of fifteen minutes anesthesia should appear in the axilla, a short distance down the inner surface of the arm, and over the third and fourth ribs. A well-defined Horner's syndrome and anhidrosis of the entire arm and the side of the neck and head should be present. The failure of these signs to develop indicates that the needles have not been correctly inserted, and a readjustment should be made. After it has been determined accurately that the needles have been properly placed, it is preferable to inject 3 more c.c. of novocaine through each in order to ensure widespread anesthesia and to make the final injection of alcohol painless. Three to 4 c.c. of 95 per cent alcohol is then slowly injected in each needle.

#### THE THYROID

Although total thyroidectomy for the relief of cardiac pain and congestive heart failure is a relatively recent advocacy, the relationship between thyroid activity and cardiac disease has been implicit in the expositions of numerous authors for over a century and a half. As early as 1786, in his original and remarkably accurate description of hyperthyroidism, Parry<sup>50</sup> observed that angina pectoris appeared months before enlargement of the thyroid gland was apparent. At the beginning of this century, Koehler<sup>51</sup> in his observations upon patients in whom his father had performed total thyroidectomy reported relief of cardiac insufficiency. Hamilton<sup>52</sup> also noticed the beneficial effect exerted upon the cardiac insufficiency by subtotal thyroidectomy in patients with hyperthyroidism. The close relationship existing between the thyroid and the heart was strongly emphasized by Lahey and Hamilton.<sup>53</sup> They directed attention particularly to such "thyrocardiacs" whose cardiac



mention a few of its disadvantages. Fortunately, these are not very significant. The effect of the alcohol is not permanent, and in some instances will necessitate reinjection. The fact that it is a procedure employing the blind injection of a destructive solution will in some cases produce certain complications. The difficulty of limiting the effect of the injected alcohol will occasionally produce a painful neuritis, and pleural injury is a constant hazard.

The technique of paravertebral alcohol injection as described by White is relatively simple. He prefers to have the patient lying on his side with the knees drawn up, the shoulder at the edge of the bed, and the head deflected forward, as in performing a spinal puncture. In our experience, it has been found more desirable to have the patient

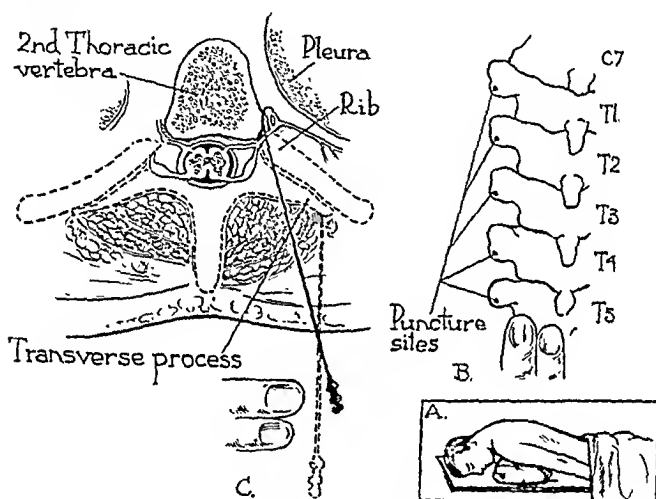


Fig. 4.—Diagrammatic representation of technique of paravertebral alcohol injection for angina pectoris. *A*, Patient lying in prone position with pillow supporting chest so as to produce hyperflexion of neck. *B*, Puncture sites are on a horizontal line approximately 2 to 2½ fingerbreadths lateral to spinous processes of the seventh cervical to fifth thoracic vertebrae, inclusive. *C*, Dotted needle indicates first position with point touching transverse process or angle of rib. Needle in solid lines indicates final correct position, which is approximately 2 fingerbreadths deeper than first position and directed medially toward midline about 20°. Point of needle is in contact with lateral aspect of body of vertebra immediately adjacent to sympathetic ganglion and chain.

lying face downward with the chest supported by pillows, as shown in Fig. 4*A*. The bony landmarks consist of the spinous processes of the seventh cervical vertebra and the first to the fifth thoracic, inclusive. In this region, the spinous processes are imbricated, and the tip of each one of these spinous processes lies at an exact horizontal level of the transverse process and the posterior angle of the rib next below, and as shown in Fig. 4*B*, the highest prominent vertebral spine, the seventh cervical, marks the level of the first rib. By means of a fine hypodermic needle an intracutaneous wheal of novocaine is formed at the points of

in whom a diseased heart was incapable of delivering an adequate flow of blood by correspondingly diminishing the metabolic demands. This could be readily done by removing the thyroid which so influences tissue metabolism.

In angina pectoris, a similar discrepancy was also found to exist between tissue demands and blood supply.<sup>67-72</sup> Thus, if one considers angina pectoris as due to insufficient blood supply to the heart when there is an increased demand upon the heart in exertion and emotion although the blood supply may be adequate during rest, presumably thyroidectomy would diminish this demand so that the previous flow through the coronaries is sufficient even during strain.

The mechanism of relief of pain immediately after total thyroidectomy is still controversial. Weinstein and others<sup>73</sup> made postoperative studies on 50 consecutive patients and found that 20 showed early relief from pain. As a result of these studies, they were led to the conclusion that this early relief from pain was due to interruption of nerve impulses from the heart to the central nervous system and was evidently a coincidental division of cardiosensory fibers at the time of operation. The anatomical and clinical basis for this concept has been recently investigated by Weinstein and Hoff.<sup>74</sup> They made observations on the immediate relief of hyperesthesia and hyperalgesia of the chest during the operation and observed that in one patient immediate relief of muscle and periosteal hyperalgesia of the chest wall occurred after the severance of the inferior thyroid vessel. In the second patient immediate unilateral relief occurred after one lobe of the thyroid was shelled out of its bed. Immediate relief of hyperalgesia occurred on the left side of the chest after the second lobe of the thyroid gland was removed. In the third patient, the results of hemithyroidectomy and block of the stellate ganglion in hyperalgesia of the chest were compared. In both cases there was loss of muscle and periosteal tenderness of the chest. They also performed anatomic dissections on 10 fetuses and 6 adults, and noticed that in 70 per cent of the dissections of the thyroid lobe the superior cardiac nerve was closely applied to the posterior surface of the lobes of the thyroid. In 20 per cent of the dissections of the thyroid lobes, the middle cardiac nerves were in apposition with the posterior surface of the lobe or the inferior thyroid vessels. They concluded that this immediate relief of pain was due to injury to the superior and middle cardiac nerves and nerve plexuses on the posterior surface of the thyroid gland and its vessels. The variability in the relationship of these nerves to the posterior surface of the lobe or its vessels corresponds to the appearance of the early relief of pain following the total removal of the thyroid gland. These observations, however, do not conform with the investigations of Langley,<sup>14</sup> Ranson,<sup>6</sup> and Ionesco,<sup>10</sup> as well as with others who strongly deny the presence of cardiosensory

failure was so predominantly obvious that it frequently masked the underlying hyperthyroidism as the "complete relief of a complete disability" which could be obtained by thyroidectomy in these patients. Christian<sup>54</sup> was one of the first to appreciate the close relationship between thyroid activity and cardiac disease and, in 1925, expressed the concept that "thyroid deficiency may be . . . a form of cardiac rest, that is advantageous to the heart." Riesman<sup>55</sup> and Boas and Shapiro<sup>56, 57</sup> and others actually performed subtotal thyroidectomy in some patients having cardiac disease but not considered as having thyroid disease. However, their results were disappointing and it was not until 1933 that Blumgart, Levine, and Berlin<sup>58</sup> made their original proposal of total thyroidectomy in the treatment of chronic nonthyrogenous heart disease.

The rationale of total thyroidectomy in the treatment of cardiac disease is based upon two factors: (1) a decrease in tissue metabolism consequent to the removal of thyroid secretions, and (2) an interruption of cardiosensory impulses which is coincident to the operative removal of the thyroid and depends upon the anatomic relationship of the cervical cardiac nerves to the thyroid gland. In the normal individual the speed of blood flow has been shown by Blumgart and Weiss<sup>59</sup> to be directly dependent upon the metabolic demands of the body. It is now a well-established fact that hyperactivity of the thyroid gland results in increased tissue metabolism, and conversely, hyposecretion of the thyroid gland produces a diminished tissue metabolism. Blumgart and his coworkers<sup>60, 61</sup> showed that in thyrotoxicosis not associated with cardiac disease there was a commensurable increase in speed of blood flow, and conversely, in uncomplicated myxedema there was a considerable decrease in speed of blood flow. Burwell, Smith, and Neighbors<sup>62</sup> and Grollman<sup>63</sup> showed that these changes in velocity were generally in proportion to the changes in basal metabolic rate and the changes in cardiac output. However, it was observed that in cardiac insufficiency and in angina pectoris this normal relationship between speed of blood flow and metabolism no longer exists. In such instances, even though the basal metabolic rate was normal, the blood flow velocity was considerably decreased. Blumgart<sup>64</sup> further demonstrated that "the velocity of blood flow through the lungs parallels in general the degree of circulatory incompetence and as such provides an objective and qualitative index of the circulation." Blumgart and his associates<sup>65, 66</sup> further showed that this speed of blood flow in uncomplicated myxedema was frequently as slow as in congestive failure when the metabolic rate was normal and there was no evidence of circulatory failure. In other words, although these patients had a decreased speed of blood flow, their tissue metabolism was correspondingly diminished also. Thus, it seemed reasonable to assume that it would be possible to relieve a patient

in whom a diseased heart was incapable of delivering an adequate flow of blood by correspondingly diminishing the metabolic demands. This could be readily done by removing the thyroid which so influences tissue metabolism.

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afferent fibers in the superior cardiac nerves. Recently, Heinbecker<sup>8</sup> has presented some evidence of cardiosensory afferent fibers in the superior cardiac nerve.

As a result of their studies on the altered sensitivity to epinephrine, Levine and his associates<sup>75, 76</sup> are of the opinion that the relief of pain immediately following total thyroidectomy is due to a lessened sensitivity to epinephrine. Because anginal attacks could be precipitated by the subcutaneous injection of adrenalin, they believe that in these patients there is an increased sensitivity to adrenalin. Following total thyroidectomy this adrenalin sensitivity disappeared. Shambaugh and Cutler<sup>77, 78</sup> produced angina pectoris in dogs by traction on the anterior descending branch of the left coronary artery. Whereas subminimal traction produced no evidence of discomfort, typical reaction to discomfort did occur after the dogs were also given intravenous injection of adrenalin. Sawyer and Brown<sup>79</sup> performed a group of experiments on cats whose hearts were denervated. Adrenalin was injected before and after total thyroidectomy. Their experiments demonstrated that removal of the thyroid decreases the response of the denervated heart to both injected and secreted adrenalin and that this is the result of a decreased sensitivity of the heart tissue following the removal of the thyroid. Bérard, Cutler, and Pijoan<sup>80</sup> recently utilized the principle that an artificially created hypoglycemia by the intravenous injection of insulin elicits a compensatory hypersecretion of adrenalin in testing the thyroid adrenal relationship in totally thyroidectomized patients. They found no material changes in arterial tension, indicating no increase in the circulatory adrenalin. Schmitker, Van Raalte, and Cutler<sup>81</sup> studied the relationship between the thyroid gland and the vasomotor apparatus by making skin temperature determinations on patients subjected to total thyroidectomy before and after operation. Their results showed that there was diminished vasomotor tone with relaxation of the smaller blood vessels, most pronounced shortly after removal of the thyroid gland. On the other hand, Riseman, Gilligan, and Blumgart,<sup>82</sup> as the result of their studies, were led to believe that there was no altered or diminished sensitivity to epinephrine following total thyroidectomy. Thus, the exact mechanism of the relief of pain immediately after operation following total thyroidectomy remains yet unsatisfactorily explained.

During the past four years, since Cutler and Schmitker<sup>83</sup> and Berlin<sup>84</sup> independently performed the first ablations of normal thyroids for heart disease, a large number of cases have been done and the results reported by numerous investigators, with a consequent better understanding of the indications, limitations, and selection of cases. The proper evaluation of any new therapeutic procedure is always difficult, because one must always rely upon the published data. Obviously, the advocates and originators of a method will be most prolific in their

writings, and their pardonable enthusiasm may unwittingly dull their critical judgment. Even a casual survey of the literature reveals distinct differences of opinion as to the value of this procedure. Such eminent surgeons as Clute,<sup>85</sup> Reid,<sup>86</sup> Tront,<sup>87</sup> and Moore<sup>88</sup> are not thoroughly convinced of the soundness and justification of the operation. Lourie<sup>89</sup> critically questions the rationale and believes that "the harm that will be brought about by the spread of these operations will greatly outweigh the possible temporary benefits." In order to form a fairer evaluation of the procedure, Parsons and Purks<sup>90</sup> tabulated data concerning all cases on whom the operation had been performed. The material was obtained from a fairly complete survey of the literature and from inquiries sent to various clinics throughout the country. Of 133 collected operations performed for angina pectoris, 71, or 55.46 per cent, showed excellent results; 36, or 28.12 per cent, were moderately improved; 5, or 3.9 per cent, were slightly improved; and 15, or 12.5 per cent, were classed as failures. The operative mortality was 3.75 per cent. These results correspond fairly closely with those reported by Weeks<sup>91</sup> in a somewhat similar tabulation of 100 cases in which the operation had been done in 26 clinics. If the excellent results and moderately improved groups are considered together as satisfactory, it will be observed that 83.58 per cent showed good results in the series reported by Parsons and Purks,<sup>90</sup> and 91.4 per cent in those collected by Weeks.<sup>91</sup> Thus, these statistics indicate that it is undeniably a distinctly valuable procedure in relieving cardiac pain. Whether the procedure prolongs life or not cannot be answered. It is admittedly a procedure attempting to relieve symptoms and not to affect cardiac pathology.

There are certain disadvantages of the procedure that must be considered in its proper evaluation. Total ablation of the thyroid is difficult in any type of case, and in these patients who are admittedly poor risks it will carry a very definite mortality. There will also be a fairly high incidence of complications. In the collected series reported by Parsons and Purks,<sup>90</sup> recurrent laryngeal injury occurred in 8.6 per cent and tetany in 10.3 per cent of the cases. Fortunately, this latter complication was of serious consequence in only one instance. It must be remembered, however, that these complications have occurred in the hands of surgeons who possess a relatively wide experience with thyroid surgery.

Another disadvantage of the procedure is the production of myxedema, as it is, in truth, the substitution of one disease for another. However, the conversion of a previously alert and active patient into the sluggish state associated with myxedema may be justified if it relieves the patient of agonizing and intractable pain. Although the undesirable consequences of artificially induced myxedema can be alleviated to some extent by the proper administration of thyroxin, in many

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extreme care in dissection. The latter authors<sup>99</sup> advise removing each lobe of the thyroid by working from that side of the patient because of the fact that in their first few cases they injured two left recurrent nerves while doing the procedure according to their previous custom of operating entirely from the right side. We<sup>101</sup> have also made a similar observation and consider this a valuable suggestion. Berlin<sup>102</sup> has called attention to the variations in the anatomic relationship of the recurrent laryngeal nerve. The fact that, in 10 per cent of the cases he studied, the recurrent laryngeal nerves partially penetrated the gland substance emphasizes the care that must be taken to visualize the nerve in order to avoid its injury while freeing the gland. Freedman<sup>103</sup> advocates direct laryngoscopy after the removal of one lobe in order to determine whether a vocal cord has been paralyzed. In order to more readily mobilize the lateral lobes, Berlin<sup>84</sup> advocates the transverse division of the infrahyoid group of muscles.

In order to diminish the surgical hazards of total thyroidectomy, some investigators have attempted to permanently lower the metabolic rate by less drastic means. Heavy doses of roentgen irradiation were employed by Friedman and Blumgart<sup>104</sup> in some patients but were without benefit and the method was abandoned. More recently, Lyon and Horgen<sup>105</sup> and Friedman<sup>106</sup> have advocated a less radical surgical procedure. They have performed and recommend ligation and division of the superior and inferior thyroid arteries. The former authors believe that this not only decreases the amount of blood entering the thyroid, but also cuts off all stimuli from the sympathetic nervous system to the gland. This procedure is sharply criticized by Blumgart<sup>93</sup> as not being a reliable substitute for total thyroidectomy, because the blood supply to the thyroid gland is derived, to an important degree, from many vessels penetrating the posterior part. He quotes the investigations of Fine and Levenson,<sup>107</sup> who, after removing the entire thyroid gland of rabbits and then replacing the gland immediately in its former position, were unable to find any changes in the metabolic rate in approximately 50 per cent of their animals. He believes that similar difficulties apply to complete separation of the thyroid gland from the autonomic nervous system.

#### COLLATERAL BLOOD SUPPLY

An entirely new principle in the surgical treatment of coronary thrombosis has been devised and advocated by Claude S. Beck.<sup>108, 109</sup> This method consists of an attempt to develop a collateral circulation by the production of a new blood supply to the heart by grafting tissues into the myocardium (Fig. 5). The rationale of this procedure is based upon the attempt to correct the decreased myocardial vascularity which invariably occurs with coronary sclerosis. It is a well-known fact that the compensatory circulatory mechanisms of the heart are dreadfully



instances it may be extremely difficult to find the optimum dosage. It must be remembered that, whereas thyroxin counteracts these effects of myxedema, in order to obtain the full benefit of the operation these individuals must be kept at a low basal metabolic rate. Hurzthal<sup>92</sup> wisely calls attention to this consideration. Adequate doses of thyroxin to obviate the effects of myxedema may cause the patient to suffer from angina, and a reduction of thyroxin to relieve the angina may cause the ill effects of myxedema.

Unquestionably, the procedure has been inadvisedly performed in many instances, but with increasing experience the criteria for the selection of patients have become more rigid. Blumgart<sup>93</sup> advises against the operation in the presence of rapidly progressive cardiovascular disease, such as malignant hypertension or syphilitic cardiovascular disease. He agrees with Hepburn<sup>94</sup> and Levine and others<sup>95</sup> that it is also unwise to operate upon patients who are in the terminal stages of the diseases. Another contraindication to operation is a low preoperative basal metabolic rate. Mixer, Blumgart, and Berlin<sup>96</sup> hesitate to operate upon those patients in whom the preoperative basal metabolic rate is below 15 per cent and consider a basal metabolic rate of 20 per cent or more a definite contraindication to operation. The presence of a recent coronary occlusion, renal insufficiency, active infection, such as bronchietasis, lung abscess, and active rheumatic involvement, are further contraindications to operation. Wolfert<sup>97</sup> is of the opinion that the operation should not be performed in patients who do not respond to medical therapy.

Although no attempts will be made here to give a detailed technical discussion of total extirpation of the normal thyroid gland, there are certain aspects of the technique which demand consideration. The procedure is not one that can be undertaken lightly and should never be performed by one who is not thoroughly familiar with the normal anatomy of the thyroid gland and its relationship to the surrounding structures as well as with the variations which may occur.

The type of anesthetic employed is of considerable importance as has been emphasized by Mixer and others,<sup>98</sup> Berlin,<sup>98</sup> Cutler and coworkers,<sup>99</sup> and others. These surgeons who have had considerable experience with the procedure insist upon the use of local analgesia. Although they employed general anesthesia in their earlier cases, they found that it proved far less satisfactory as it abolished the cough reflex and thus increased the danger of pulmonary complications. However, Murtagh<sup>100</sup> still prefers general anesthesia because it obviates mental anxiety and avoids the use of adrenalin which may induce an attack of angina. Cutler and others<sup>99</sup> also consider local analgesia more desirable because it permits easier determination of injury to the recurrent laryngeal nerve during the operation. Avoidance of injury to recurrent laryngeal nerves and of the parathyroid glands necessitates

three weeks anastomoses between the grafts and the heart could be demonstrated. These anastomoses were demonstrated<sup>114</sup> by the presence in the myocardium of a dye previously introduced by way of the graft and also by injecting a solution of barium sulphate<sup>115</sup> into a coronary artery and tracing the location of the solution in the chest by roentgenograms.

In another interesting group of experiments it was found that the vascular graft could act as a protective measure against sudden complete occlusion of one of the coronary arteries.<sup>116</sup> Of ten normal dogs in which the coronary artery was ligated, 7, or 70 per cent, died within a very short time. In 12 dogs in which a collateral vascular bed had been previously developed, ligation of the coronary artery produced death in only 4, or 33.3 per cent. In another group of experiments it was found that after giving the heart a collateral vascular bed it was possible to completely occlude the right and both major branches of the left coronary artery by doing the occlusion in four or five stages. In this manner the only blood supply to the myocardium from the coronary was from the small septal branch which comes off above the bifurcation of the left main stem. In another group of experiments, Beck and his coworkers showed the importance of an equal distribution of blood to the myocardium. If the right and both major branches of the left coronary arteries were occluded to about one-third of their cross-section in one stage, the animals would recover. On the other hand, if the four or five peripheral branches of the coronary artery over the apex of the left ventricle were completely ligated in one stage, ventricular fibrillation always developed. It can be readily observed that the total coronary blood flow in the former group of experiments is considerably less than in the latter, yet it was in the latter group that a fatal termination always occurred. Beck and his collaborators believe that the significance of these experiments is the extreme importance of the maintenance of uniform distribution of blood flow. These investigators believe that a collateral vascular bed effects an equal distribution of blood to the myocardium by transporting blood from extracardiac sources into the myocardium and from one part of the heart where the circulation is good to another part of the heart where the circulation is deficient.

Emboldened by these propitious experimental investigations, Beck and his collaborators<sup>115</sup> attempted their application in cases with coronary sclerosis, and it was done in collaboration with their cardiologist, Dr. Harold Feil. The operation was performed for the first time on a patient with coronary sclerosis on February 13, 1935. This patient was a white male laborer, twenty-eight years of age, who had typical sub-sternal pain of two years' duration and was finally forced to give up his work. The patient made an excellent recovery from the operation and

inadequate. This is due to the peculiar anatomic arrangement of the vascular supply of the myocardium. The myocardium has only two coronary arteries. When one of these arteries becomes occluded, compensatory adjustments are made either through the other artery, by way of the thebesian channels, or through the anastomoses with the aorta which exist in the fat at the base of the heart. Such compensatory mechanisms are obviously inadequate as attested by the fearful mortality in coronary disease. Thus, it becomes apparent that the addition of other anastomotic channels to the heart might change the previously inadequate compensatory mechanism to one that is adequate. It was with such reasoning that Beck<sup>110</sup> began his experiments in February, 1932.

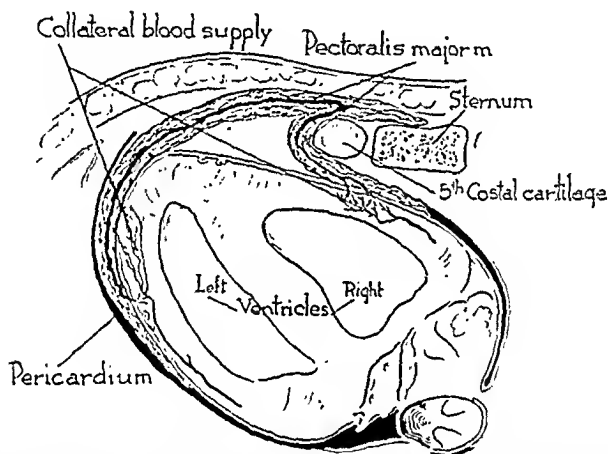
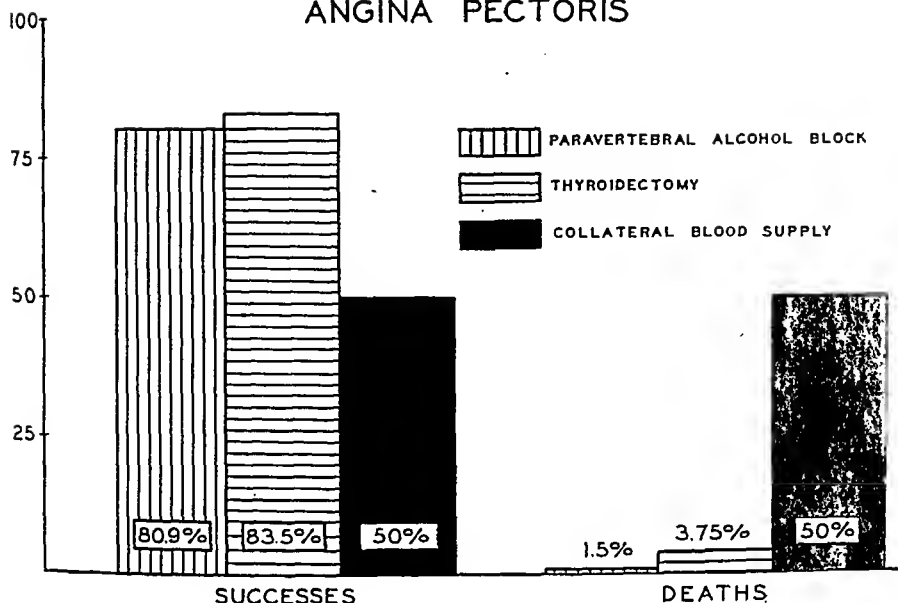


Fig. 5.—Diagrammatic representation of method of increasing collateral blood supply to the heart according to Beck's procedure. The pectoral muscle is used as a pedicle graft with one portion of it attached to the right ventricle and another portion to the left ventricle.

Although this investigator fully appreciated the Herculean task confronting him, there were two facts which suggested the feasibility of this procedure. Hudson and others<sup>111</sup> demonstrated the presence of blood vessels in the fat at the base of the heart anastomosing the coronary system with branches of the aorta; and Moritz, Hudson, and Orgain<sup>112</sup> established the existence of blood vessels in pericardial adhesions. Further experimentation was then necessary in order to determine: (1) whether it was possible to deliberately produce these anastomotic channels, and (2) whether they could serve a functional purpose.

Beck<sup>113</sup> and his coworkers first produced a collateral vascular bed by destroying the mesothelial envelope around the heart by roughening the lining of the parietal pericardium and the epicardium. Various tissues, such as fibrous pericardium, pericardial fat, pedicle grafts of pectoral muscle, and omentum, were used for the new vascular bed and within

## ANGINA PECTORIS



Graph IV.—Comparison of the results obtained by three methods of treatment in coronary artery disease and cardiac pain. The figures on paravertebral alcohol block are based upon 68 cases reported by White<sup>29</sup> and Marvin<sup>49</sup>; those on thyroidectomy are the results obtained in a series collected by Parsons and Purks,<sup>50</sup> and the results on collateral blood supply were reported by Beck.<sup>116</sup>

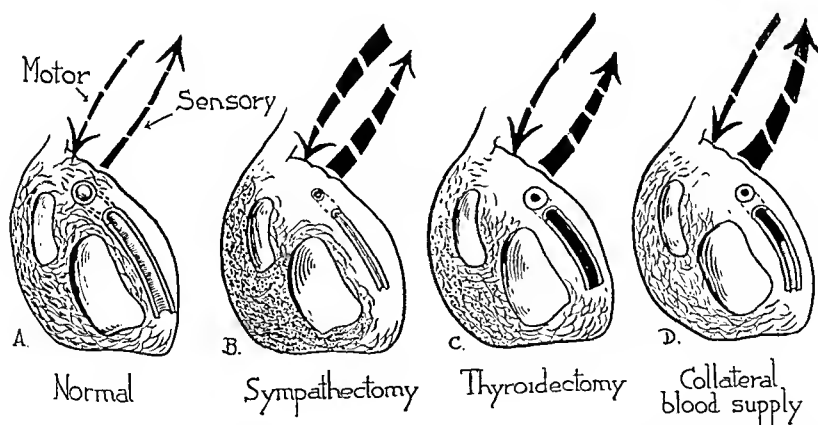


Fig. 6.—Diagrammatic representation of therapeutic procedures indicated in various types of coronary disease. A represents a normal heart with normal musculature and vascular supply. The thickness of the arrows represents normal degrees of motor and of sensory cardiac innervation. B represents the type of case in which a therapeutic attack upon the sympathetic nervous system is indicated: (1) cases in which there is increased cardiosensory and motor sympathetic innervation which is associated with vasoconstriction and considerable pain; (2) cases in which there is marked fibrosclerotic myocardial changes indicative of advanced cardiac disease which contraindicates more formidable procedures. C represents type of cardiac lesion in which thyroidectomy is indicated. There is some fibrosis of the cardiac musculature and occlusion of coronaries, which is due to thrombosis rather than to vasoconstriction. These patients have an angina of effort rather than emotion as in B. There is also an increase in the cardiosensory innervation. D represents the type of case in which collateral blood supply is indicated. The cardiac musculature is little involved, and the thrombosis and occlusion of the coronaries are not extensive.

for the past year has been employed as a gardener, doing the work of a man in good health. He has no pain and takes no drugs.

In his most recent communication, Beck<sup>116</sup> states that he has performed the operation upon 16 patients, with a mortality of 50 per cent. This is undeniably a frightfully high mortality and may appear almost unwarranted. However, in justification, the author states that this was an extremely bad group of patients with advanced stages of coronary sclerosis. They were patients who had previously concluded that there was nothing to risk because life without improvement was not worthwhile. However, the author feels that this mortality must necessarily be reduced in order to make the operation practical. He is of the opinion that this can be accomplished; first, by a careful selection of patients who do not have a too far advanced coronary sclerosis, and second, by reducing the magnitude of the operation. The latter factor, he believes, has already been accomplished to some extent, as is discussed below in a consideration of the technique. In the last 5 patients in whom this was done, there were no operative deaths. In his concluding remarks, the author opines that in general the results seem sufficiently good to encourage further development of the subject. He considers this procedure a direct attack upon the coronary sclerosis with the purpose of giving the myocardium additional blood supply, and thus preserving the heart function. Its concern with angina pectoris is only secondary. However, in those patients who survived there was complete relief of pain in several, and in the remaining there was marked relief of pain. There was also an apparent increase in the functional capacity of the heart.

The technical procedure consists of grafting part of the pectoral muscle upon the myocardium. The skin incision is made transversely over the precordium, and the pectoral muscles are separated from the chest wall by blunt dissection. Whereas originally Beck employed a bilateral approach to the heart by the removal of two costal cartilages on each side of the sternum, he has since simplified it and utilizes a unilateral approach. The pectoral muscle is transected laterally about four inches from the sternum to make a graft with the pedicle attached along the sternal margin. The fifth and sixth costal cartilages are removed, care being taken to avoid injury to the mammary vessels, and the parietal pericardium is opened. By means of a burr the lining of the parietal pericardium and epicardium is roughened. The author states that they have attempted to avoid such trauma to the epicardium because it initiates extrasystole, and refers to the observations of Mautz,<sup>117</sup> who found that the application of cocaine directly to the surface of the heart will block these impulses. He states also that in several of the patients powdered beef bone was placed in the pericardial cavity for the purpose of producing a low grade foreign body reaction. The muscle graft is

suited for the collateral blood supply method are represented in Fig. 6 D. The cardiac musculature is little involved, and the thrombosis and occlusion of the coronaries are not extensive.

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divided into two parts by incising parallel with its fibers along the lower margin of the third rib, and the upper part of the graft is placed beneath the sternum to the right ventricle, while the lower is applied to the left ventricle. The pericardial cavity is then left widely open so that the adjacent vascularized tissues are in contact with the anterior aspect of the heart.

The three main methods of attack in the surgical treatment of coronary artery disease and cardiac pain have been considered and discussed. Obviously, the enthusiastic advocates of each method will paint a glowing picture of the advantages of their method and will have a pardonable tendency to dim their disadvantages. Thus, a proper evaluation may be extremely difficult. Probably each method has its appropriate place in the treatment of this important disorder, and a critical analysis may aid us in determining which type of patient is best suited for each method.

If an attempt be made to compare the advantages and disadvantages of the three methods from the standpoint of successful results and mortality, the graphic illustration (Graph IV) reveals that thyroidectomy has a slight advantage over paravertebral alcohol block and that both have a marked advantage over collateral blood supply. On the other hand, the mortality from paravertebral alcohol block is practically negligible with thyroidectomy having a mortality two and a half times as high. The mortality of 50 per cent in the collateral blood supply method makes it undeniably a formidable procedure.

Because these three surgical methods of attack have different rational bases and because coronary artery disease and cardiac pain vary in their pathologic physiologies, it may be possible to indicate in which type of patient each method may be most suitable. We have attempted to illustrate this diagrammatically (Fig. 6). Fig. 6 *A* represents a normal heart with normal musculature and vascular supply. The thickness of the arrows represents normal degrees of motor and of sensory cardiac innervation. In comparison to this, Fig. 6 *B* represents the type of case in which a therapeutic attack upon the sympathetic nervous system is indicated: (1) cases in which there is increased cardiosensory and motor sympathetic innervation which is associated with vasoconstriction and considerable pain; (2) cases in which there is marked fibrosclerotic myocardial change indicative of advanced cardiac disease which contraindicates more formidable procedures. Fig. 6 *C* represents type of cardiac lesion in which thyroidectomy is indicated. There is some fibrosis of the cardiac musculature and occlusion of coronaries, which is due to thrombosis rather than to vasoconstriction. These patients have an angina of effort rather than emotion as in *B*. There is also an increase in the cardiosensory innervation. The patients who are probably best

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bundles. A large dressing is applied, open drainage is maintained, but no drainage tubes are inserted at the time of operation. The patient rests on his back in a semisitting position. On the third day Penrose drains are inserted. The operation is recommended by the author because of its simplicity, the adequacy of drainage, and the almost total absence of sucking in the thoracotomy wound.

**Dr. Harold Neuhof**, of New York City, has employed free transplants of fat for the closure of pulmonary cavities remaining after the evacuation of destructive suppurative lesions. These cavities may range in size from very small defects to a lattice lung occupying much of a lobe. They are featured by bronchial fistulas, and if they do not heal spontaneously, they may be simple and easy of solution, or they may be difficult and complicated. The free transplant of fat has been employed in seventeen cases and was successful in eleven. The author admits that the use of free fat transplants, in the presence of infection, is a violation of principles of tissue transplantation that have been laid down in the past, but he advocated the method on the basis of clinical trial. The mechanism of healing of the cavities following the use of fat transplants is not as yet clearly understood.

**Dr. Harry C. Ballou** and **Dr. Alton Goldbloom**, of Montreal, reported on their experiences with prontosil and prontosil in the treatment of hemolytic streptococcus infections of the lung, pleura, and chest wall. The drugs were administered orally and intramuscularly. Intravenous administration was formerly used but has been discontinued. The oral dosage has been limited to sixty grains per day. The authors conclude that the dyes possess definite chemotherapeutic properties in the presence of acute and chronic infections due to the hemolytic streptococcus. Case reports were presented and a particularly striking result occurred in an apparently hopeless infection of the pleura, chest wall, and ribs complicating scarlet fever.

**Dr. D. A. Wood** and **Dr. Leo Eloesser**, of San Francisco, discussed the rôle of the dual pulmonary circulation in various pathologic conditions of the lungs. They reviewed the literature on the subject and presented a study based upon seventy-two injections of specimens. The authors conclude that increase in bronchial circulations occurs in (a) hypertrophic processes in pulmonary parenchyma; (b) obstructive lesions, pulmonary and cardiac, sclerotic, congestive, etc; (c) inflammatory lesions, chronic and acute; pulmonary, cardiac, and mixed; (d) processes of debatable etiology, emphysema, asthma, etc.; and (e) congenital anomalies. They found that dilatation of the bronchial artery occurs in primary pulmonary malignancy but not in metastatic tumors of the lungs. Hemorrhage occurs in primary neoplasms, but not in secondary. In ligation to control hemorrhage it may be necessary to occlude both the pulmonary and bronchial vessels. In such an instance a ligature is placed around the entire hilum, but not sufficiently tight to occlude the bronchus.

**Dr. William S. McCann** and **Dr. Nolan L. Kaltreider**, of Rochester, New York, reported on the effect of thoracoplasty on the pathologic physiology of respiration. They made measurements of the total pulmonary capacity and its subdivisions in chronic cases of pulmonary tuberculosis treated by thoracoplasty. In addition roentgenographic studies were made; the gaseous content of the arterial blood was determined. The venous pressure and blood velocity were measured and in six instances respiratory response during exercise was determined. These measurements were made from 7 to 127 months after operation. They found that thoracoplasty caused a marked reduction in total and vital capacity, the diminu-

# Review of Recent Meetings

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## REVIEW OF THE TWENTIETH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THORACIC SURGERY, SARANAC LAKE, N. Y., MAY 31, JUNE 1 AND 2, 1937

HERBERT A. CARLSON, M.D., MINNEAPOLIS, MINN.

*(From the Department of Surgery, University of Minnesota)*

THE outstanding feature of the meetings was an address by Professor Hans C. Jacobaeus, of Stockholm, Sweden, on *Bronchspirometry and Its Use in Determining Indications for Thoracoplasty in Bilateral Pulmonary Tuberculosis*. Jacobaeus has devised a double-barrel bronchoscope with which he can occlude the trachea and the right main-stem bronchus in such a manner as to provide separate channels of breathing for each lung. Recordings are made on two spirometers, one for each lung, so that the amplitude of respiration, the oxygen intake, the carbon dioxide output, minute ventilation, ventilation equivalent, and vital capacity of the two lungs may be compared. The functional test of the lungs obtained in this manner often gives one information not determined by x-ray examination or by any other method. No serious accidents have attended the use of this method.

Jacobaeus concluded from his bronchspirometry studies that pneumothorax in many instances, although it reduces the vital capacity, does not materially alter the efficiency of the lung in oxygenating blood. He found that in some instances the lung for which thoracoplasty was proposed was carrying the greater share of the respiratory load. Frequently the apparently healthy lower lobe which one attempts to preserve in performing thoracoplasty has very little functional value. In addition to its use in pulmonary tuberculosis, the method was employed in a study of cases of bronchiectasis and lung cyst.

Experiments were also carried out in which one bronchus was obstructed, or in which one lung was required to breathe nitrogen. In these cases it was found that the unobstructed lung takes over the function of both.

The presidential address was given by Dr. Leo Eloesser, of San Francisco, on *Bronchostenotic Cavities and Other Closed Foci of Tuberculous Suppuration in the Lung*. In this address the many phases of the subject were considered, somewhat in detail; illustrative cases were described in which contrast media had been injected through external openings. One of the important conclusions was that the obstruction of a bronchus to a tuberculous cavity is not necessarily beneficial as is often assumed, but that it may be harmful due to the blockage of drainage of a suppurative process.

Dr. Frank S. Dolley, of Los Angeles, read a paper on the treatment of ruptured lung abscess. He treats massive pyopneumothorax following sudden rupture of a lung abscess by complete and immediate drainage of the empyema cavity. A large thoracotomy is provided by resection of ribs and excision of intercostal

pneumoneetomy. Studies were made upon a litter of six puppies. Adult dogs were also studied. Three of the puppies were pneumoneetomized at the age of one month (the entire left lung being removed); the remaining three animals were kept as controls. Six months after pneumoneetomy, all of the animals were subjected to strain experiments. These consisted of treadmill tests, anoxemia tests, and lung volume determinations. Observations were repeated at monthly intervals throughout the growth period. The authors concluded that true hypertrophy of the lung, rather than emphysema occurred in the young subjects. Furthermore, the younger the subject, the less was the respiratory embarrassment after pneumoneetomy.

Dr. William H. Stewart and Dr. F. H. Ghiselin, of New York City, gave a beautiful demonstration of ciné fluorographie studies of thoracic diseases. By ciné fluorography is meant the making of a motion picture record of the image seen on the fluoroscopic screen. The difficulties surrounding this procedure have been greatly lessened by new developments in apparatus. Advantages of the method are that moving organs may be intensively studied at leisure as long as desired without undue exposure of the patient or the operator to the x-ray. It is relatively inexpensive and uncomplicated and furnishes a good library for teaching purposes. It is especially valuable in all lesions above the diaphragm. In this demonstration the film showing the pulsation of an aortic aneurysm and another showing the movement of lipiodol in a case of bronchiectasis were particularly dramatic.

Dr. Harold Brunn and Dr. H. B. Stephens, of San Francisco, gave a report of the successful removal of a carcinoma of the esophagus, together with a review of the cases treated at the University of California Hospital. The patient suffered from a moderately advanced carcinoma involving the midesophagus. The technique of Torek was employed. The value of preoperative pneumothorax, positive pressure, intratracheal anesthesia, and the prevention of a contralateral pneumothorax were stressed. The patient made a successful operative recovery.

Dr. Herman J. Moersch, of Rochester, Minn., discussed the successful treatment of carcinoma of the esophagus by means of surgical diathermy. A case of squamous cell carcinoma of the esophagus affecting a man sixty-eight years old was reported. The growth was destroyed by means of surgical diathermy in 1935. The patient is alive and well, with no evidence of local or metastatic recurrence of the growth, able to eat everything without difficulty and has gained twenty-one pounds.

Dr. Stuart W. Harrington, of Rochester, Minn., presented a moving picture demonstration of the management of teratoid tumors of the chest. He stressed again the value of the posterior incision in removing the majority of these teratoid tumors. He also emphasized the importance of early removal partly because of the fact that some of these tumors become malignant.

Dr. C. S. Beck, Dr. F. R. Mautz, and Dr. A. B. Moritz, of Cleveland, discussed the augmentation of collateral coronary circulation by operation. In the normal heart abundant anastomoses exist between the major branches of the coronary arteries and extracoronary arteries. There is considerable natural variation in the degree of such anastomosis, but functionally the coronary arteries are end arteries. As a result of chronic progressive obstruction of coronary arteries the intercoronary and extracoronary anastomoses enlarge. Symptoms of coronary disease are interpreted as failure of collateral blood supply to compensate for the disease. The Beck operation is designed to improve the collateral coronary

tion being roughly proportional to the number of ribs resected. The reduction in the midcapacity and the residual volume were less marked for the other capacities, resulting in high normal values for the relative values. The ability to expand the chest in patients with thoracoplasty was greatly diminished. Its usual interference with the chest cage results in a slight or moderate anoxemia. In spite of the presence of arterial anoxemia, no evidence of polycythemia was found. The value for the venous pressure was slightly elevated but was not abnormally high. In about half the patients the velocity of the blood was slightly delayed. During moderate physical exertion patients with thoracoplasty operations had a rapid and shallow type of breathing compared with normal individuals. The expression "total ventilation" was abnormally high, and all but one patient complained of dyspnea on moderate exertion. The pulmonary reserve was reduced in all cases. Definite correlation existed between the degree of disability and the reduction in the vital capacity and the pulmonary reserve and the increase in the expression total ventilation. The authors conclude that thoracoplasty is more disabling than pneumothorax for the amount of lung collapsed.

Dr. Richard H. Overholt and Dr. John S. Harter, of Boston, reported on further observation on the lung volume after thoracoplasty. They found that thoracoplasty results in an irreversible and permanent alteration of the volume of the thorax. Lung volume and vital capacity determinations were made in a series of seventy-two thoracoplasty subjects. One-half of them have now been restudied six to eighteen months after completion of the operation. The results show alteration in the lung volume in both directions. Increase in the volume of the lung after operation was sometimes found to be as high as 24 per cent above the preoperative readings. The majority of cases showed a slight decrease in lung volume. The vital capacity in all cases showed a decrease of 8 to 30 per cent. The study suggests that the more nearly the operation approaches the ideal, i.e., selective collapse with preservation of functioning basal portions, the less change there is in the respiratory reserve.

Dr. Adrian Lambert, Dr. Frank Berry, Dr. W. Dickinson, Dr. J. Richards, and Dr. Andre Cournand, of New York City, discussed the methods for estimating pulmonary and circulatory capacity. Mechanics of breathing were studied by the use of respiratory tracings, lung volume and maximum capacity determinations, as well as by the more common methods of fluoroscopy, x-rays, and external chest measurements. Respiratory gas exchange was estimated by gasometric methods, analysis of expired air and of the arterial blood gases. Circulatory mechanics were studied by measurement of circulation time, venous and arterial blood pressures, and by the response of these and of the vital capacity to intravenous saline injection. In order to test the efficiency of breathing, the adequacy of the gas exchange, and the circulatory adjustments in changing physiologic conditions, these measurements were carried out at rest, during one minute of moderate exercise and during the period of recovery from exercise. It was found in these studies that ventilation may be reduced in emphysema even if the volume of the lung is increased. Illustrative clinical cases were presented.

Dr. B. N. Carter and Dr. J. J. Longacre, of Cincinnati, reported a study of changes in cardiorespiratory physiology following total pneumonectomy in young developing animals. The purpose of the paper was to determine the degree of compensatory return of function in young pneumonectomized animals and to contrast this degree of return of function with that in adult animals following

bacteria was decreased. It was also found that the operator and his assistant are carriers of *Staphylococcus aureus* in many instances, and that the gauze mask affords little protection. The author compared the results obtained in 110 thoracoplasties performed without sterilization of the air in the operative field with 100 similar operations performed in a field of sterilized air. The number of infections was reduced, the severity of infection, and the postoperative temperature elevations and durations were also reduced, and the general reaction of the patient was less when this method of sterilization was employed.

Dr. H. R. Decker, of Pittsburgh, reported on his experience with collapse therapy for pulmonary tuberculosis in the fifth and sixth decades. Of 200 patients in this series, 20 per cent were well and able to do some work, 25 per cent were improved, 25 per cent were unimproved, and 30 per cent were dead. The author found that the older patients do fairly well with phrenic nerve operations, closure of cavities occurring in 15 per cent. The beneficial results from phrenic nerve operations are in direct proportion to the extent of rise in the diaphragm.

Pneumothorax was less successful in younger patients. One reason for this is that a larger percentage have adhesive pleuritis, and here again there is a greater reduction in the vital capacity. Patients in this age group, however, should be treated vigorously by pneumothorax, but pneumothorax should be discontinued soon if collapse is unsatisfactory. The extent and duration of pneumothorax are important factors in the success of treatment.

One of the points particularly stressed in this report was the high mortality (27 per cent), in the thoracoplasty cases.

Dr. Owen H. Wangenstein, Dr. H. A. Carlson, and Dr. Warner F. Bowers, of Minneapolis, reported on partial thoracoplasty for pulmonary tuberculosis with a suggested plan of operation, including preliminary anterior chondrocostectomy, together with a review of the results. In the series of cases reported a preliminary anterior chondrocostectomy was performed which permitted removal of the upper three or four costal cartilages, together with a short segment of rib. About ten days later the upper-stage posterior operation is performed at which time the upper three ribs are completely removed. The complete excision of the ribs is greatly facilitated by the preliminary anterior chondrocostectomy. Additional operations are performed subsequently as required in the individual cases. Forty-seven patients operated upon in this manner were reported. There were two deaths in this series, but no deaths occurred after the upper-stage operation. Ten of the patients, in addition, had the extrafascial apicolysis described by Semb. Patients were followed six months to three years after operation. More than half of the patients had both closure of cavity and negative sputum at this time.

Dr. B. P. Potter, of Secaucus, N. J., discussed the management of the excessively mobile mediastinum in the surgical collapse of tuberculous pulmonary cavities. This paper dealt with a study of sixty patients in whom the mediastinum was fixed by artificial methods either during the course of pneumothorax or prior to thoracoplasty. The studies have been conducted for the past five years, and there has been a follow-up of from two to five years. The author believes that shifting of the mediastinum is a factor in the spread to the opposite lung. Shifting of the mediastinum also resulted in dyspnea, tachycardia, weight loss, and gastrointestinal complaints. Fixing of the mediastinum diminishes the risk of thoracoplasty. Methods that have been employed for fixing the mediastinum consisted of injecting gomenol, 2 to 5 per cent, in amounts varying from 10 to 15 c.c.;



circulation in coronary disease. The mechanisms by which this may occur are: 1. Development of new intercoronary anastomoses to aid in the redistribution of blood in the myocardium. 2. Development of new extracoronary anastomoses to increase the total blood supply of the heart. 3. Increase in caliber of existing intercoronary and extracoronary anastomoses by hyperemia and tissue reaction.

Dr. Alfred Blalock and Dr. Sanford E. Levy, of Nashville, Tenn., gave a paper on tuberculous constrictive pericarditis with a report of cases treated by pericardectomy. Nineteen patients with chronic constrictive pericarditis were studied. The disease was believed to be tuberculous in origin in 16 patients and was proved to be tuberculous in 13. Pericardectomy was performed in 12 of the 19 patients; of these, 8 were proved to be tuberculous. The authors reported that of the patients with tuberculous pericarditis treated by pericardectomy, the early results were good.

Dr. Ralph Adams and Dr. Edward D. Churchill, of Boston, reported six cases of the syndrome situs inversus, bronchiectasis and chronic sinusitis. The frequency with which this association occurs in the hospital population is entirely beyond the possibility of mere chance. Embryologic theories as to the cause of situs inversus suggest that the bronchiectasis may be due to associated maldevelopment.

Dr. E. C. Drash, of University, Va., gave a paper on an appraisal of closed intrapleural pneumonolysis in pulmonary tuberculosis. The report was based on a series of more than two hundred personal cases and a survey of the literature. He stressed the importance of waiting until there is a fairly stable intrapleural pressure, usually requiring at least three months. The results were much the same as those that have been reported elsewhere. The author included among his complications several cases of tuberculous empyema occurring several months after the operation.

Dr. William F. Rienhoff, Jr., of Baltimore, described a two-stage operation for total pneumonectomy demonstrating a new technique for closure of the bronchus. In the first stage, through an anterior incision, the pulmonary artery is ligated; at the second stage, the pneumonectomy is completed. Emphasis was placed upon the dissection of the lymphatic glands. The author closed the bronchus by a new method. In this method a flap, prepared from the membranous portion of the bronchus, is folded over and sutured to the edges of the bronchial stump. This method may also be applied in the removal of the lower portion of the trachea. In the discussion that followed, Dr. E. D. Churchill presented arguments for the employment of lobectomy rather than total pneumonectomy for carcinoma. It was his belief that if carcinoma has already invaded the mediastinal nodes, even total pneumonectomy is futile. He, therefore, recommended that whenever the tumor appears to be limited to one lobe, lobectomy should be performed rather than risk the higher mortality of pneumonectomy. The question of thoracoplasty following total pneumonectomy was also discussed by Dr. Rienhoff and by Dr. Evarts Graham, and they both appeared to be of the opinion that thoracoplasty to obliterate the pleural cavity on the operated side is a desirable procedure.

Dr. Deryl Hart, of Durham, N. C., reported further on his experience with sterilization of the air in the operative region with bactericidal radiant energy. A study made to determine the number of bacterin in the air in the operating room demonstrated that after sterilization by ultraviolet light the number of

in the Treatment of Intestinal Tuberculosis, by Dr. Mack McConkey; The Lymphatics of the Pleura in Relation to Cold Abscesses of the Chest Wall, by Dr. Hugh E. Burke; Immediate and Late Results of Hygienic-Dietetic Treatment of Pulmonary Tuberculosis, by Dr. Homer N. Sampson and Dr. Fred H. Heise; Venous Pressure in Collapse Therapy and Other Complications of Pulmonary Tuberculosis, by Dr. John Steidl.

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## REVIEW OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF GOITER, DETROIT, MICH., JUNE 14, 15, AND 16, 1937

WALTER G. MADDOCK, M.D., ANN ARBOR, MICH.

*(From the Department of Surgery, University of Michigan)*

WITH the objective of bringing together each year men who will present the best that has been thought, said and done in the study of goiter and its allied problems, the association held its annual three-day conference in Detroit. Dr. Nelson M. Percy, of Chicago, as president of the Association, was chairman of the meetings. Dr. Frank Lahey, of Boston, was elected president for the ensuing year.

The following is a summary of the papers read:

**The Thyrocardiac**, by Dr. Nelson M. Percy, Chicago: In this address by the president of the Association, attention was called to the group of patients who have cardiac failure with hyperthyroidism. To aid in the diagnosis of this condition the following suggestions were made: First, any elderly patient with auricular fibrillation and a palpably enlarged or hard thyroid gland is a thyrocardiac and a candidate for thyroidectomy, unless proved otherwise. If mitral stenosis underlies the auricular fibrillation, the indication is even more clear. In the author's experience, 90 per cent of the cases of auricular fibrillation seen were due to hyperthyroidism. Second, any elderly patient presenting the symptoms of decompensation and having a palpably enlarged, firm or nodular gland should be considered a thyrocardiac and a candidate for thyroidectomy, unless proved otherwise. Third, in any case of failing health in a middle-aged to elderly patient, in which the entire clinical picture is not obviously due to another condition, some degree of hyperthyroidism should be suspected. Fourth, we should be goiter conscious. When looked for, hyperthyroidism will be discovered in many patients where it was never suspected before.

In the management of the thyrocardiac before, during, and after the operation all of the special considerations common to the care of middle-aged individuals with debilitating disease were shown to be necessary, and conducive in many cases to most brilliant results.

**Revised Concepts of the Thyroid and Metabolism in Pregnancy**, by Dr. G. C. Shaufler, Portland, Ore.: The general purpose of this paper was to indicate the actual confusion of thought on the relationship of the thyroid to female sex function. An appeal was made for closer cooperation between the obstetrician and the surgeon and internist particularly interested in the goiter problem, so

mineral oil, in amounts varying from 10 to 15 c.c.; hypotonic salt solution, 7 per cent, in amounts up to 150 c.c. The oil or solution employed is injected into the pleural cavity, the patient lies on his sound side for one hour after the injection. Within twenty-four hours a small to moderate effusion usually develops. The temperature may be elevated, but usually returns to normal within seventy-two hours. The mediastinum must be retained in the desired position, and in some cases, it is necessary to withdraw air or fluid. Fixation is complete when no shift occurs with expiration following deep inspiration. Further injections of the liquid may be required in some cases. In the presence of adhesions there are dangers in injecting the oil. It was stated that the pleura thickened only moderately, and this thickening does not interfere with reexpansion of the lung in pneumothorax.

Dr. Fred R. Harper, of Tucson, Ariz., reported on the effect of phrenic nerve interruption on the gastrointestinal tract. He found that gastrointestinal symptoms developed following paralysis of either the right or left hemidiaphragm. The syndrome following paralysis of the left diaphragm is characterized by loss of appetite, fullness, nausea, and vomiting. Following a paralysis of the right hemidiaphragm, the characteristic symptom is primarily pain in the right upper quadrant. Roentgenograms taken before and after phrenic interruption show anatomic changes in the abdominal viscera sufficient in degree to explain the symptoms. Temporary phrenic interruption is advised in preference to permanent phrenic exeresis because in all of the observed cases the symptoms did not persist after the function of the diaphragm returned. The author felt that 25 per cent of the symptoms occurring were detrimental to the patient.

Dr. Pol N. Coryllos, of New York City, reported on the study of tuberculous empyema based on 150 personal cases. He found that tuberculous empyema is more likely to occur in the presence of a positive pressure in the thorax, and that a subpleural tuberculous focus is invariably present. When the oxygen in the pleural space is increased and the carbon dioxide is decreased, it is an indication of the presence of a bronchopleural fistula. The gas analysis test is of great value as it occurs prior to any other evidence of fistula. Dr. Coryllos classified tuberculous empyema into three groups: (1) the pure tuberculous empyema, with a positive sputum; (2) the pure tuberculous empyema with a negative sputum; and (3) the mixed empyema with either a positive or a negative sputum. He stressed the value of early thoracoplasty particularly in the first and third groups.

Dr. W. W. Woodruff, of Saranac Lake, N. Y., also gave a review of the results of treatment of tuberculous empyema. He found that oleothorax is sometimes effective in pure tuberculous empyema, but of no value in mixed infections. A patient with mixed infection has about one-half as good a chance to recover as one with a pure tuberculous infection. Bronchial fistula is an indication for drainage in tuberculous empyema. Of thirty-eight patients who had no surgical treatment for tuberculous empyema, 40 per cent are well and working, and 40 per cent are dead.

Additional short papers were presented by the physicians of Saranac Lake, N. Y., on the following subjects:

The Virulence of the Tubercle Bacillus Destroyed by the Action of the B. Macerans and the L. Pentoaceticus, by Dr. H. A. Bray and Dr. Joseph Kurung;  
The Importance of Determining the Vitamin C Content in Fruits and Vegetables

in the Treatment of Intestinal Tuberculosis, by Dr. Mack McConkey; The Lymphatics of the Pleura in Relation to Cold Abscesses of the Chest Wall, by Dr. Hugh E. Burke; Immediate and Late Results of Hygienic-Dietetic Treatment of Pulmonary Tuberculosis, by Dr. Homer N. Sampson and Dr. Fred H. Heise; Venous Pressure in Collapse Therapy and Other Complications of Pulmonary Tuberculosis, by Dr. John Steidl.

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that a greater unanimity of opinion concerning the care of thyroid disturbances during pregnancy should result. In the past two years the author has abandoned iodine administration to obstetric patients and because of frequent findings suggesting mild hypothyroidism among these patients has substituted desiccated thyroid therapy. The results were reported as justifying this treatment.

**The Relationship Between Hyperthyroidism and Hyperparathyroidism**, by Dr. Andre Crotti, Columbus, Ohio: Decalcification of the skeletal system during thyrotoxicosis has been noted for years. In over 50 per cent of the cases presented there was an average increase of 60 to 65 per cent in the calcium and phosphate elimination in the urine. In many patients definite symptoms result from this abnormality; joint pains, often excruciating, are not uncommon as a consequence of the subperiosteal decalcification, the pain being due to spicules of bone remaining. There may be profound muscular asthenia. In one case of long-standing, severe thyrotoxicosis coming to autopsy, typical changes of osteitis fibrosa cystica along with a fractured femur and normal parathyroid glands were found. This skeletal process was considered to be due to hyperparathyroidism induced by an overactive thyroid gland. Thyroid surgery produces a marked improvement or elimination of the decalcifying process.

**Some Prognostic Criteria in Selection of Cases of Exophthalmic Goiter for Nonsurgical Treatment**, by Dr. Saul Hertz, Boston: This report was a follow-up study of 24 patients first presented before the Society five years ago. Of the 24, 12 have since had thyroid surgery, 2 could not be traced, and on further study 1 appeared not to have a toxic goiter. The remaining 9 have been carried along on medical treatment; their basal metabolic rates have dropped below normal as a rule, and all except one have gained weight. All 9, after five years, are still free from evident hyperthyroidism. Additional cases have been followed in the meantime. As a prognostic test for candidates for medical management a drop of 15 to 20 per cent in the basal metabolic rate on iodine therapy was considered important. The patients selected had mild hyperthyroidism, were without evidence of cardiac damage or other complications which would require surgery, and as a group had an initial basal metabolic rate of less than plus 35 per cent. It was understood that medical treatment was indicated, and carried out, only when the physician had close contact with his patient, enabling him to see the patient at frequent intervals.

**Iodine Response and Some Other Factors in Relation to Mortality in Thyrotoxicosis**, by Dr. J. Lerman, Boston: In a series of 1,187 patients with toxic goiter seen at the Thyroid Clinic of the Massachusetts General Hospital, of whom 731 had adequate metabolic data, it was found that 3.4 per cent (25 patients) failed to respond to iodine. The mortality in the nonresponding group was 24.0 per cent; whereas, the mortality in the patients responding to iodine was 1.1 per cent. While an analysis of several factors did not adequately explain the failure to respond to iodine, it did show that a large portion of the mortality in this group occurred in elderly patients, running relatively low metabolisms and possessing nodular goiters and some form of heart disease. It was hoped that by concentrating one's effort on this small group of patients who do not respond to iodine the mortality in toxic goiter could be appreciably lowered.

**Normal and Abnormal Iodine Metabolism—Its Relation to the Reticulo-Endothelial System**, by Dr. Joseph L. De Courcy, Cincinnati: Evidence was presented by this author to show that blood iodine is not always increased in cases

of hyperthyroidism. This was interpreted to indicate that it is not the thyroid alone which controls iodine metabolism and regulates the level of blood iodine. The liver plays an important rôle in iodine metabolism, and in conditions in which the liver is damaged—as in cholecystitis and liver disease—blood iodine is increased and reaches a higher level than in hyperthyroidism. Recent animal experiments confirming these findings were discussed and were believed to indicate that it is the reticulo-endothelial system, especially the reticulo-endothelial cells of the liver—the Kupffer's cells—that primarily control iodine metabolism. The thyroid gland was thought to act as a stimulator of the reticulo-endothelial system rather than directly on iodine metabolism.

The findings were considered to indicate that the determination of the iodine content of the blood is valuable as a test of liver function rather than of thyroid function and that it may be so used clinically in surgical cases where liver damage is to be feared.

**Recurrent Hyperthyroidism**, by Dr. Norris W. Gillette, Toledo: The avoidance of persistent and recurrent hyperthyroidism should start at the time of the primary operation. Much grief to the surgeon and discomfort to the patient can be obviated at this time. A radical resection of all the tissue which may be degenerated will prevent many recurrences. When this complication does make its appearance, the patient should be treated first medically by adequate iodination, rest, and sedatives. Where this treatment is inadequate, surgery should be reemployed. The first procedure should be eradication of all possible remnants of thyroid tissue, following which, if the patient still suffers from hyperthyroidism, a denervation of the adrenals may be employed.

**Needless Thyroid Surgery, An Analysis of One Hundred Cases**, by Dr. A. S. Jackson, Jackson Clinic, Madison, Wis.: This study reviewed 100 patients for whom thyroidectomy had been advised, but for whom on proper study the following disease conditions were found to be responsible for the disorder:

Nervous exhaustion	45
Physical exhaustion	21
Menopause	15
Miscellaneous	6
Colloid goiter	5
Septic tonsils	5
Psychosis	3
	<hr/> 100

Errors in the metabolic rate test were frequently contributory to the original error in diagnosis. Such tests must not be taken too literally except after repeated trial and with due regard for the attitude and condition of the patient at the time of the test. In case of doubt, an iodine test is often of great value and the failure to respond to it rules out exophthalmic goiter, provided the patient is not iodine fast. Two out of three patients having toxic adenoma respond favorably to iodine; one-third are made worse. In the absence of hyperthyroidism, a favorable response to iodine does not occur. The conditions found to be the proper diagnosis for the hundred patients reported may in some ways simulate hyperthyroidism, but can be and must be differentiated if needless thyroid surgery is to be avoided.

**Comparative Anatomy and Physiology of the Thyroid Gland**, by Dr. George Crile, Cleveland: The animals of the air, the earth, and the waters were all included in this interesting correlation of data on the thyroid, the adrenals, and

the brain. Man was pointed out to have a greater amount of thyroid than adrenal tissue in order to keep up his energy, not for a sudden burst in an emergency, but for continuous steady work such as no other animal can do. The cetaceans also—whales, porpoises—have larger thyroids than adrenals in order to keep up a high continuous oxidation for the supply of plenty of heat as a protection against their cold environment. All the other animals have adrenals larger than the thyroid.

In a search for some law of oxidation in the animals, the weight of thyroid glands, then of the adrenals, and finally of the thyroid plus adrenals plus brain was compared with the heat production. No correlation was found. When the brain weight alone was compared, a correlation was found: "One gram of brain tissue is associated with or requires the production of 12.5 Cal. in 24 hours, allowing  $\pm 20$  per cent variation." This law excepted only man and the cetaceans.

The brain is the spark plug governing the rate of energy. If the brain is large, the thyroid has to be large to supply the continuous energy needed.

**The Urinary Iodine in Thyroid Disease**, by Dr. George M. Curtis and Dr. Italo D. Puppel, Department of Research Surgery of Ohio State University, Columbus, Ohio: Dr. Curtis' presentation of this subject was both authoritative and instructive. The daily urinary excretion of iodine in central Ohio was shown to average 51 micrograms, the variations from 36 to 78 micrograms being found due to a noneconstant diet. For the inhabitants of five nongoitrous regions the normal urinary excretion of iodine was four times that of the inhabitants of five goitrous regions. This observation was considered to have a definite bearing upon iodine deficiency as related to the incidence of goiter. The form in which iodine is excreted has not been definitely determined, but from evidence so far it is in a more simple compound than thyroxine.

The majority of patients with hyperthyroidism have an increased loss of iodine in the urine, part of which is suspected of originating in an increased breakdown of the high iodine-containing thyroid hormone. Iodine from other tissues may be a source. Following thyroidectomy for various forms of goiter there occurs an increased loss of iodine in the urine, even for uniodized patients. It was surprising to find that following other operations—thoracoplasty, radical mastectomy, and spinal fusion—a similar increased loss of iodine occurs. It appears that a part of this postoperative loss of iodine comes from the tissues. The urinary iodine can be considered as having a significance in thyroid disease similar to that of urinary sugar in diseases of the pancreatic islets or urinary calcium in diseases of the parathyroids.

**Clinical and Experimental Observations on Parathyroid Transplants**, by Dr. Herman K. Pinkus, Dr. Walter G. Maddock, and Dr. Frederick A. Collier, University of Michigan, Ann Arbor, Mich.: In a review of the literature, fifty-nine cases of parathyroid transplants to humans were found. Twenty-three were done for the relief of chronic postoperative tetany and in only nine of those was improvement noted for a year or more, observation beyond that time generally recording a relapse. To possibly adapt the graft to the host, in two female cases of postoperative parathyroid tetany the parathyroid graft was first cultured for two weeks in a medium made up in part by the host's blood plasma, and then implanted. No improvement of the tetanic condition was noted in either of these cases. In a series of parathyroid homeotransplantations on white rats, poorer results were obtained when tissue culturing was employed between the taking of the graft and its implantation than when the

implant was made immediately. Clinically and experimentally, tissue culture did not improve the results of parathyroid homeotransplantations.

**Interpretation of Basal Metabolic Rates in the Relatively Normal Individual**, by Dr. Walter Boothby and Dr. W. A. Phummer, the Mayo Clinic, Rochester, Minn.: A presentation was given of the use of the Gaussian curve and the standard deviation in medicine. Their value was apparent in discussing the variability of the basal metabolic rate of an individual, between individuals, and between individuals with and without metabolic disease. On the basis of extensive data, the normal basal metabolic rate was found to be  $\pm 13$  per cent for males and  $\pm 18$  per cent for females. A further application of these mathematical aids was the determination of how many patients would fall in any given group and what proportion would be abnormal.

**Evidence That Most Thyroid Disease Is Congenital**, by Dr. William B. Patterson, Dr. H. F. Hunt, and Dr. R. E. Nicodemus, Geisinger Hospital, Danville, Pa.: Blood cholesterol studies revealed that rabbits, unlike human beings, develop a hypocholesteremia in the second and third trimesters of pregnancy. Total thyroidectomy in the nonpregnant rabbit produces a hypercholesteremia, but in the pregnant rabbit the usual hypocholesteremia results. Since the maternal thyroid gland had been removed, the observed increase in maternal metabolism was considered to be due to the absorption of large amounts of thyroxin from the fetus. That this resulted in hypothyroidism in these fetuses was shown by the fact that their blood cholesterol was over 100 per cent higher than that of fetuses of normal rabbits. Also, the thyroid glands of fetuses of thyroidectomized rabbits were in a state of extreme hyperplasia in an unsuccessful effort to maintain normal fetal metabolism. The investigators considered that this hyperactivity before normal thyroid structure had been reached would in all probability produce permanent damage to the thyroid.

From blood cholesterol determinations on pregnant women and the infant at birth, it was found that when maternal hypothyroidism and hypercholesteremia exist, fetal hypothyroidism and hypercholesteremia are also present. Histologically, the human thyroid at birth is in a state of hyperactivity. There is little doubt that the fetal thyroid reacts to fetal hypothyroidism by hyperactivity and hyperplasia just as does the rabbit fetal thyroid. In later years, depending upon the iodine supply and the physiologic demands, the effect of this early strain may lead to clinically evident thyroid disease.

**The Production of an Increase in Metabolic Rates of Thyroidectomized Rabbits by Certain Pituitary Extracts**, by Dr. D. K. O'Donovan and Dr. J. B. Collip, McGill University, Montreal: Studies on the metabolism of rabbits, both normal and thyroidectomized, indicated that pituitary extracts contain a metabolic stimulant which in its time relation differs from the thyrotropic hormone. This substance produced a rapid, transient rise in metabolism soon after its injection and was considered to be closely related to or identical with the melanophore hormone.

**The Management of Minor Complaints After Thyroidectomy**, by Dr. Howard M. Clute and Dr. Hollis L. Albright, Boston: The authors presented a discussion of the following minor disturbances after thyroidectomy: (1) difficulty in breathing and swallowing; (2) changes in voice; (3) injuries to the superior and inferior laryngeal nerves with resultant changes in function of the muscles of the



larynx, pharynx, and soft palate; (4) poor scars; and (5) deformity of the contour of the neck. Methods to avoid or to treat these complications were presented in detail.

**The Effect of Iodized Salt After Twelve Years' General Use Upon the Incidence of Goiter Operations in Southern Michigan**, by Dr. Roy D. McClure, Henry Ford Hospital, Detroit: The conclusions of this author were briefly as follows: (1) In Michigan an existing deficiency of iodine in the diet can best be combated by the use of iodized salt. (2) When first used in Michigan, this iodized salt apparently increased the number of thyroid operations, possibly by activating a number of quiescent adenomas, for the increase occurred in the adenoma group. (3) The increase reached its peak in the second year after the introduction of iodized salt. From the Board of Health statistics, an increase in the death rate from goiter reached its peak in this second year. (4) Following the second-year peak the number of operations for toxic diffuse and toxic nodular goiter rapidly and steadily decreased, excepting for a slight increase during the last three years. (5) The incidence of endemic goiter has been reduced almost to nil by the use of iodized salt, and no ill effects have been noted. With no endemic goiter, toxic nodular goiter and toxic diffuse goiter are less apt to occur. (6) As publicity concerning iodized salt has fallen off, its sale has decreased. As a result, a few more goiters are seen in the school children and the number of goiter operations has slightly increased. (7) To combat this slump, greater publicity for iodized salt is needed; or should a law be passed making it mandatory for grocers to sell only iodized salt?

**Unexpected Postoperative Hyperthyroidism**, by Dr. Ambrose L. Lockwood, Toronto: The postoperative death of two patients operated upon for adenomatous goiter was reported. In one there was no evidence and in the other only slight evidence of hyperthyroidism preoperatively, so that the fatal termination in thyroid crisis was unexpected. Factors possibly contributing to the death of these patients—traction on the carotid sheath, epinephrine, ligation of large capsular veins, interference with liver function, and saturation with iodine—were discussed. The formation of a mortality committee within the Association for the recording of all deaths after thyroidectomy was suggested in the hope that by some sort of correlation greater knowledge concerning these unexpected deaths would result.

**Further Observations on Malignancy of the Thyroid**, by Dr. C. W. Mayo, Rochester, Minn.: This paper was chiefly concerned with the three-, five-, and ten-year survival rates of the 737 cases of malignancy of the thyroid gland seen at the Mayo Clinic from 1907 to 1936, inclusive. The three methods of treatment considered and the statistics were as follows:

TREATMENT	TOTAL CASES	SURVIVAL PERIOD		
		3 YR.	5 YR.	10 YR.
Thyroidectomy	112	63.6%	62.6%	52.9%
Thyroidectomy with irradiation	261	80.1%	73.7%	58.6%
Irradiation only	183	25.8%	20.7%	12.2%

From these data, thyroidectomy with irradiation was pointed out to be the most favorable method of treatment. In fairness it was mentioned that 40 per cent of the cases treated by irradiation alone were of a grade 4 type by Broder's classification. From a prognostic standpoint the papillary type of malignancy was most favorable, particularly if the growth was within an adenoma.

**Malignant Adenoma of the Thyroid With Recurrences in the Cervical Veins,** by Dr. Allen Graham, Cleveland Clinic, Cleveland: An interesting presentation was made on a selected group of four thyroid neoplasms in which the primary operation was followed by the development of local recurrences in the veins of the neck, without detectable evidence of distant metastases. The clinical findings were of adenomatous goiter and in only one case was malignancy suspected at the time of the operation. On pathologic examination the striking feature suggesting future trouble was the presence of tumor cells or tissue in the lumina of capsular veins. Postoperatively, many months passed before local recurrences were noted, and they tended to remain localized. This was consistent with the low order of malignancy in the primary tumor and in contrast to rapidity of recurrence and dissemination of highly malignant undifferentiated or diffuse carcinomas. In patients returning with a localized mass in the thyroid area two or three years or more after the removal of a thyroid tumor of low grade malignancy, recurrence in the veins should be kept in mind, and if possible, a complete, wide excision of the mass should be done.

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## REVIEW OF THE AMERICAN SURGICAL ASSOCIATION MEETING, NEW YORK, N. Y., JUNE 3, 1937

ALTON OCHSNER, M.D., NEW ORLEANS, LA.

THE president's address by Dr. Graham, entitled **Dr. Gross Looks In on the American Surgical Association**, was splendid and excellently presented. Dr. Gross returned to attend the meeting of the American Surgical Association fifty-eight years after its founding and conversed with Dr. Graham during the presentation.

The first paper, by Frederick W. Bancroft, Margaret Stanley-Brown, and Erwin Chargaff (New York) on **Postoperative Thrombosis and Embolism**, was based on studies made by the authors since 1928. They believe that in addition to dehydration, stasis, and trauma, which are important factors in the causation of thrombosis and embolism, there are also biochemical factors. Some persons are apparently potential clotters; whereas, others are potential bleeders. It is desirable to determine those patients who are potential clotters, because it is in this type of individual that postoperative thrombosis occurs. Postoperatively the plasma-clotting index is determined as follows: The normal plasma-clotting time which is 105 seconds is used as the numerator and the patient's clotting time is used as the denominator. Normally the index figure should be 0.8 to 1.05. Patients with values below 0.8 are potential bleeders; whereas, those with values above 1.05 are potential clotters. An increase of the calcium of the blood does not tend to produce coagulation. In their study they have made routine determinations both preoperatively and postoperatively to determine the potential clotters. For the postoperative treatment they have used early exercise of the lower extremities, the prevention of ileus and abdominal distention by means of the duodenal tube, the avoidance of tight bandages, the administration of food early in order to stimulate peristalsis, and the prevention of dehydration. In those patients in whom the test shows a potential clotting, a diet high in carbohydrates and low in proteins is given. Sodium thiosul-

phate, 10 c.c. of a 10 per cent solution, is given every day for four to five days. In their early series, approximately 34 per cent of the cases had a high index. In more recent series employing new tests, 12 per cent to 14 per cent of patients examined were potential clotters. By the institution of prophylactic measures in instances in which the plasma-clotting index is high, they have been able to decrease materially the incidence of thrombosis.

Dr. John Homans (Boston), in discussing the paper, stated that he felt that it was desirable to pay more attention to the physical measures in the prevention of thrombosis than the biochemical measures suggested by the authors. He advises elevation of the lower extremities postoperatively, and the avoidance of the sitting posture, because this apparently decreases the rate of blood flow through the venous system.

Dr. Howard Lillenthal (New York), in discussing the paper, suggested the use of leeches not only as a curative procedure, but also as a prophylactic one, and stated that he uses four leeches on the fifth to the ninth day in all of his abdominal operative cases.

Dr. Charles C. Lund (Boston) presented a paper on *Embolectomy in Peripheral Embolism* in which he reported 55 cases of peripheral arterial embolism, most of which were associated with heart disease. About 90 per cent of the patients had auricular fibrillation. About half the patients had mitral stenosis; whereas, the remainder had arteriosclerotic heart disease. Although there is frequently some confusion in differentiating between thrombosis and embolism, Lund is of the opinion that whenever a sudden occlusion of an artery occurs it is always produced by embolism. Included in his series were all cases of sudden blockage of the major vessels of the periphery which were admitted to the hospital within a week after onset. Approximately half the cases had the onset of embolism before admission to the hospital; whereas, the others had their onset while in the hospital and most of them occurred on medical service. Twenty-three cases had been operated upon, 30 operations in all being done. There was a 44 per cent mortality rate, and 37 per cent obtained good functioning results. In more recent series, the mortality rate has been lower and the incidence of good results has been higher. In the 29 cases in which no operation was done mortality rate was 85 per cent and the successes were only 8 per cent. Lund concluded from his observations that embolectomy was not justified in upper extremity embolism, because the reestablishment of circulation occurred in every instance whether embolectomy was done or not. In cases of embolism involving the lower extremity, however, embolectomy should be done and done early, because the danger of developing gangrene is great. This is particularly true in embolism of the iliac and femoral arteries.

In discussion, Dr. Harry Kerr (Washington, D. C.) reported a case of saddle embolism at the bifurcation of the aorta which he operated upon by an abdominal section. The embolus was removed and the patient did well until the eighth day when there was a recurrence of the embolism. This time he approached the embolism by exposing the femoral artery under local anesthesia and sucking out the clot from below. He states that he has used it in one arm case with good results.

Dr. Albert Singleton (Galveston) reported a case of embolism of the brachial artery in which at operation it was found that the clot extended below the site at which the artery was opened. This was removed by massaging the arm from

below upward. After closing the artery, there was no return of the pulse. However, the artery was again opened and this time a small needle was introduced into the radial artery at the wrist and the artery flushed out with sodium citrate solution which ended in a good result.

Dr. Edwin Beer (New York) reported four saddle emboli cases. One was operated upon transabdominally and ended fatally. In two others the clots were sucked out by means of a well-lubricated catheter introduced into the femoral artery, but both patients succumbed. One of these showed the futility of attempting to remove a saddle embolus through the femoral because the clot extended up to the diaphragm. A fourth case was not operated upon, and the patient recovered with the loss of one great toe.

Dr. I. A. Bigger (Richmond) had had two cases with saddle emboli. One resulted in extensive gangrene of both legs and the other was operated upon fifteen hours after onset. It was his intention to open the aorta, but this was impossible because of the extensive calcification. One of the iliacs was opened and the clot sucked out. The operation was unsuccessful and gangrene subsequently developed.

Dr. Lund in closing the discussion stated that he had not seen any saddle emboli, but that he had had two bilateral cases. In both of these the emboli were removed through the femoral, one successfully and the other unsuccessfully. He prefers to approach an embolus from below than from above. With regard to the ultimate outcome of these patients and whether the operation was desirable, even in patients with heart disease, he states that in the Swedish embolectomy series one-fourth of the patients died within the first year, one-half died within three years, one-third were alive after five years, and one-eighth were alive at the end of ten years. These results are good enough to warrant the operation.

Dr. E. R. Schmidt and Dr. Ralph Waters (Madison, Wis.) in discussing Anesthesia and Surgery stated that the difficulty in obtaining anesthesia is directly proportionate to the metabolic rate. Preoperative medication lowers the metabolism and fright, emotion, fever, and thyroid activity increase it. By knowing the various planes of anesthesia and at which plane the various reflexes are abolished, it is possible for the anesthetist in cooperating with the surgeon to keep the patient at the optimum plane of anesthesia. Whereas a prolonged operation with the patient under light anesthesia is relatively safe, a short operation with the patient in deep anesthesia is dangerous. Clamping and pulling of the peritoneum produces a reflex which requires a deep anesthesia and should be avoided in closing the abdomen. Careful cooperation between the surgeon and anesthetist is important.

Dr. Waters in discussion stated that the anesthetist occupied a place between the surgeon and the laboratory and that he could be of great value to the surgeon in reducing morbidity and mortality.

Dr. A. W. Elting (Albany, N. Y.) stated that in the past there has been relatively little interest in anesthesia and he feels that a new era is being opened. The need for places for training for anesthetists is becoming greater, and with the increased number of well-trained anesthetists, anesthesia will improve.

Dr. Howard C. Naffziger, Dr. Frederick Foote, and Dr. Jesse Carr (San Francisco) discussed Obstructive Jaundice: The Cause and Prevention of the Bleeding Dyscrasia. Sulfur compounds in the blood of humans and animals with jaun-

phate, 10 c.c. of a 10 per cent solution, is given every day for four to five days. In their early series, approximately 34 per cent of the cases had a high index. In more recent series employing new tests, 12 per cent to 14 per cent of patients examined were potential clotters. By the institution of prophylactic measures in instances in which the plasma-clotting index is high, they have been able to decrease materially the incidence of thrombosis.

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blood pressure following the clamping of the blood supply to the transplanted kidney, this did not remain elevated. Because the hypertension did not remain when the transplanted kidney was maintained ischemic, they believe that the renal nerves play no rôle in elevation of the blood pressure following clamping of the renal artery but that they may play a rôle in maintaining it.

In discussing these three papers, **Dr. Alfred W. Adson** (Rochester, Minn.), stated that clinically many mistakes had been made in the surgical treatment of patients with hypertension, as the methods and patients had to be chosen by trial-and-error methods. Many of the patients were relieved, however, although many were not. They have done three types of procedures. Rhizotomy was done in 37 cases. Most of the cases which they have operated upon, however, have been treated by resection of the splanchnic nerves and the first lumbar ganglia. This treatment has been used in 87 cases. Unless they have gotten a definite decrease in the blood pressure to within normal limits by the use of conservative measures such as rest in bed, the use of amyl nitrate and barbiturates, they feel that the operation should not be done. In their series of cases, they have only had two deaths, those occurring in the patients having rhizotomy.

In closing the discussion **Dr. Heuer** stated that their results had differed from Adson's in that in several cases which had not responded well to the conservative measures they were agreeably surprised to obtain beneficial results following the rhizotomy.

**Dr. Walter E. Dandy** (Baltimore) discussed **Intracranial Pressure Without Brain Tumor: Diagnosis and Treatment**. During the past seven years he has observed twenty-one cases which have offered diagnostic and therapeutic problems. These patients have been admitted to the hospital with the diagnosis of brain tumor. All had the symptoms of brain tumor, such as headache, vomiting, double vision, and dizziness. In every instance there was an increase in the cerebrospinal fluid pressure. In differential diagnosis brain tumor and optic neuritis must be considered. The diagnosis is made by ventriculography. The treatment of the condition consists of decompression which gives permanent relief. One of the characteristics of the condition is that the pressure is likely to vary, there being a rapid increase in the pressure, subsequently followed by a relatively rapid decrease. The cerebrospinal fluid is otherwise normal. The cause is not known. Its course is unchanged by fluid intake and also by fatigue. **Dr. Adson**, in discussion, suggested that the condition may be due to an encephalitis. **Dr. Wilder Penfield** (Montreal) asked whether the condition was not due to an increase in the subdural fluid content resulting from a mild inflammatory reaction, in which condition there is always an increased protein content of the fluid. **Dr. Dandy** in answering this question stated such was not the case, because in each instance the fluid was under the arachnoid.

**Dr. Claude Beck** and **Dr. Frederiek Mautz** (Cincinnati) presented **Control of the Heart Beat by the Surgeon**, in which the effects of atmospheric pressure, torsion, traction, angulation, and various stimuli on the heart were graphically shown. They showed that the exposure of the heart to atmospheric pressure increased the venous pressure from 4 to 6 cm. of water, which normally would do no harm but which might be very detrimental to the diseased heart. Torsion and angulation of and pressure on the heart greatly increased the venous pressure. Traction in the direction of the long axis produced little change, both on the venous and the arterial pressures. By stimulating the heart electrically with

dico increase the tendency toward bleeding. The two substances which are most likely to increase the hemorrhagic tendency are cysteine and methionine. Animals with jaundice produced by ligating the common duct if fed on a high protein diet exhibit an increased hemorrhagic tendency; whereas, if they are fed on low protein and high carbohydrate diet, there is a decreased tendency to hemorrhage. Whereas the normal plasma-sulfur content is about 70 mg. per 100 c.c., in jaundiced animals it is elevated to from 80 to 100 c.c. In a series of patients the normal plasma-sulfur value varied from 50 to 60 mg. per 100 c.c., but in patients with jaundice, it varied from 50 mg. to 130 mg. In the presence of jaundice it is important not to administer a high protein diet, but the patient should be fed a high carbohydrate diet, and in order to facilitate and accelerate the sulfur metabolism, they should receive glucose intravenously.

Dr. Waltman Walters (Rochester, Minn.), in discussion, stated that in addition to the intravenous administration of glucose it is important that the jaundice be relieved by operative measures. He believes that bleeding has become an unimportant cause of death in jaundice, as relatively few of their cases which they have lost have been from this cause.

Dr. Roscoe Graham (Toronto) stated that Ivy bleeding time is important as a test for a hemorrhagic tendency in jaundice. He does not operate upon patients with jaundice unless the Ivy bleeding time is less than four minutes.

The experimental production of hypertension was discussed in three excellent papers. Dr. Dallas Phemister and Dr. Keith Grimson (Chicago) studied the early and remote effects of total and partial sympathectomy on experimental hypertension. They found that hypertension produced experimentally by means of partial obstruction of the renal artery was not affected permanently by total sympathectomy. Following total sympathectomy there were no changes in the blood volume or the blood viscosity, but the cardiac output was definitely decreased. The temporary lowering of the blood pressure following various types of sympathectomy was always followed by a rise to the normal preoperative level.

Dr. Alfred Blalock and Dr. Sanford Levy (Nashville) studied the renal hypertension produced experimentally in dogs by the application of clamps to the renal vessel. They found that as long as some of the blood supply in the kidney remained intact, even only through the ureteral vessels, the increase in pressure did not remain, definitely showing that a pressor substance was formed in the ischemic kidney which caused an increase in blood pressure. This was demonstrated best in a transplantation experiment in which one kidney was transplanted into the neck, the renal artery and vein being anastomosed to the carotid and jugular vein, respectively, and in which the other kidney was removed. In this way all of the nerve supply to the kidney was removed. Partial occlusion of the renal artery supplying the transplanted kidney caused an increase in the blood pressure, showing that the pressor substance was formed in the kidney in which the blood supply was diminished. The resection of the splanchnic nerves and partial adrenalectomy as suggested by Adson were unsuccessful in relieving the hypertension thus produced.

Dr. George Heuer, Dr. Frank Glenn, and Dr. Charles Child (New York) also produced hypertension experimentally by constricting the artery of a single transplanted kidney. In their experiments a kidney was transplanted into the lumbar region and the renal vessel anastomosed to the femoral vessels. The Goldblatt clamp was applied to the femoral vessels after the transplantation following the removal of the opposite kidney. Although there was an increase in the

were not fixed there were no deaths. They are of the opinion that every patient with a cancer of the lip should have a prophylactic dissection of the neck in order to obtain a cure.

**Dr. James Ewing (New York)** spoke on **The Development of the Laboratory Service in a Cancer Hospital**. The importance of cancer institutes and cancer hospitals was stressed, because only by the study of a large number of adequately supervised cases in one institution can advancement in understanding and the treatment of cancer be made. By such studies, it is possible particularly in many of the transitional tumors to determine their true nature. Aspiration biopsy has been condemned as dangerous by many, but Ewing believes that it is a reliable and valuable procedure, particularly when done properly as is performed in the large cancer hospitals. It is necessary in the large cancer hospitals to have the services of the preclinical and fundamental sciences, such as physics, chemistry, physiology, and pathology.

**Dr. John J. Morton (Rochester, N. Y.):** **The Etiology of Cancer in the Light of Our Present Knowledge**. The knowledge concerning the cause of cancer is derived from three sources: first, the natural occurrence in human beings and the relationship to apparent inciting agents; second, the production of cancer in certain occupational diseases, such as radium and x-ray; and third, the experimental production of cancer in animals. The inciting factors of cancer are first physical, second chemical, and third biological. All the processes which produce cancer start within the cell. This is a self-perpetuating mechanism and one which is no longer dependent upon or related to the inciting factor. The fundamental intercellular changes might be due to hereditary constitution, chemical changes, and other factors.

**Dr. Leo Eloesser (San Francisco)** in **The Treatment of Some Abdominal Cancers by Combined Radiation and Caustery Incision** presented a moving picture of cases in which at the time of operation the small intestine was packed out of the way and protected so that the large intestinal cancer could be irradiated with the abdomen open.

**Dr. Joe Vincent Meigs (Boston):** **Cancer of the Cervix Treated by the Roentgen Ray and Radium**. A series of 70 cases of carcinoma of the cervix treated by roentgen ray and radium is reported, of which 35 per cent are living and well without disease for three and one-half years. Only 11 per cent were early cases. The technique which the authors have used in the Pondville series consists of the use of a definite amount of radium given in two equally divided treatments in the cervical canal only and given four days apart immediately after irradiation by roentgen ray is finished. The x-ray is given through four portals of entry, each field receiving a total of 1,500 to 2,000 r. units. This is usually completed in an average of fourteen days. Daily exposures of from 300 r. to 600 r. are used, alternating the field, so that a given area receives an exposure every fourth day. At each application of radium 1,500 milliecurie hours are given. On the morning of the fourth day a similar dose is reapplied to the cervical canal, making a total of 3,000 milliecurie hours applied to the cervix in two divided treatments, four days apart. This method of therapy has given very good results and produces little reaction. Often following roentgen ray treatment the tumor becomes smaller, firmer, and less infected. Nineteen (27 per cent) showed a real shrinkage of the tumor following x-ray treatment. Grade II cancers showed a greater percentage of shrinkage of tumor than did Grade III.

**Mr. Geoffrey Keynes (London)** discussed **The Place of Radium in the Treatment of Carcinoma of the Breast**. The operative treatment of cancer of the



faradic current, it was possible to produce extra systoles. By using a stronger current, it was possible to produce ventricular fibrillation which resulted in the immediate fall in the blood pressure to a dangerous level. If this were allowed to continue, the heart dilated until it extruded from the thorax, and the animal ultimately died. By massaging the heart manually, however, it was possible to increase the tone of the heart muscle, and to increase arterial blood pressure so that the corneal reflex returned. By shocking the heart electrically it was possible to reestablish the normal rate of the heart in about half the instances. After applying cocaine or meteyanine to the surface of the heart it was possible by shocking the heart to reestablish the normal rate of the heart in every instance. Dr. Beck suggests the availability of electrical connections and the use of meteyanine and cocaine in all operations on the heart because of the possibility of establishing a normal rate in individuals in whom ventricular fibrillation occurs during the operation and from which they would otherwise not recover.

Professor Henri Coutard (Paris) discussed **Cancer and Radiation: Results and Methods of Treatment**, and reported 46 cases of lymphosarcoma treated with x-ray with 34 per cent five-year cures; 66 cases of palatonsillar tumors of which 32 per cent were cured; 126 tumors of the larynx with 24 per cent five-year cures; 225 tumors of the pharynx with 11 per cent cures; and 8 cases of inoperable epithelial tumors of the maxillary sinus with 50 per cent five-year cures. Most of their cases of maxillary sinus epithelioma were treated by surgery and radium implantation. Nine hundred and eighty-four cases of uterine cervical cancer treated by x-ray and radium, using x-ray first, followed by radium implantation, gave 31 per cent five-year cures. Ninety-seven were in Group I, with 60 per cent; 336 in Group II, with 50 per cent; 411 in Group III, with 24 per cent; and 112 in Group IV, with 5 per cent five-year cures. In cancer of the tongue, interstitial irradiation, external radiation, and surgical removal of the glands of the neck were used. There were 382 cases with 18 per cent five-year cures. One hundred and ninety-eight cases of cancer of the anterodorsal region of the tongue gave 22 per cent cures. Ninety-one cases with cancer in the posterodorsal region gave only 10 per cent cures. There were 93 infralingual tumors with 18 per cent cures. Radiation affects both the tumor itself and the vasculocconnective tissue by destroying the cancer cell in the former instance, whereas, in the latter there is likely to be a fibrosclerotic transformation of the vasculocconnective tissue. In the undifferentiated tumors, irradiation is likely to be followed by success, particularly if it is located in loose connective tissue, but when located in dense muscular tissue because of the fibrosclerotic transformation of the vasculocconnective tissue, viable cancer cells may remain in fibrous tissues. In the differentiated cells, as in adenocarcinoma of the breast, the results from x-ray or radium are likely to be poor. Differentiated tumors, particularly in areas in which connective tissue is dense, are best treated by surgery. Preoperative irradiation is desirable; postoperative irradiation should be reserved only for recurrence. Adenocarcinoma is much more difficult to cure by irradiation than is stratified epithelium. In those cancers of the lip in which the cells are differentiated, the cervical glands are removed operatively.

Dr. Vilray P. Blair and Dr. J. B. Brown (St. Louis) in discussing **The Treatment of Cancer of the Mouth and Lip** stated that the treatment of cancer of the tongue is best done by interstitial irradiation. Buccal mucosal carcinomas are best treated by surgery. Prior to 1932, they did one-stage resections of the primary tumor and the cervical glands with a 33 per cent mortality rate. Since this time they have performed two-stage operations and in those cases in which the neck glands

were not fixed there were no deaths. They are of the opinion that every patient with a cancer of the lip should have a prophylactic dissection of the neck in order to obtain a cure.

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breast has not been very satisfactory and because of this the author has resorted more and more as time has gone on to radium irradiation. He does not believe in Handley's conception of cell permeation but is of the opinion that cancer spreads entirely by lymphatic embolism. In 1922, he began using radium interstitial irradiation in cancer recurrences. In 1924, he began treating inoperable primary tumors of the breast. He treated 50 inoperable cases and at the end of eight years had 10 per cent of them living and well. He now treats earlier cases of cancer with interstitial radiation. He frequently removes the tumor or breast followed by irradiation but never does an axillary dissection. In those cases in which he examined the removed tumor nine months or more after the irradiation, he found that 50 per cent of the cases showed no remaining tumor cells. He felt because the other 50 per cent showed viable cells that the large bulk of the tumor had prevented complete destruction, and that in such instances when the tumor was large it was best to remove the tumor before irradiation. The radium needles are placed in the plane between the breast and the muscles, but from his experience he is convinced that removal of the axillary gland is unnecessary. It may actually do harm in those cases in which the glands are large and is unnecessary in those cases in which the glands are small or absent. He advocates local excision of the tumor when the tumor is small or when the diagnosis is uncertain to be followed by irradiation of the breast and axilla. If the tumor is large, simple removal of the breast without removal of the muscle followed by irradiation is done. The results obtained are about the same obtained from surgery because death is due to distant and not to local metastases. In all he has had 325 cases, 250 of which were followed from 1924 to 1934. There are 85 cases in which the disease was localized to the breast, of which 83.5 per cent were well after three years, and of which 71.4 per cent were well after four years. There were 91 cases in which the disease was localized in the breast and axilla, of which there were 51.2 per cent three-year cures and 29.3 per cent five-year cures. There were 74 cases which were definitely inoperable, of which there were 34.1 per cent three-year cures and 23.6 per cent five-year cures. As the axilla was not exposed in his cases, it is probable that in many of the cases in which he assumed there was no axillary involvement such actually had occurred, so that, correcting for this error, he believes that the three- and five-year cures should be 94.8 per cent and 86.3 per cent, respectively. Irradiation is much better than operation, because it is attended with a much lower mortality rate, and there is less danger of dissemination of the disease when it has once gotten in the axillary nodes.

**Dr. S. W. Harrington (Rochester, Minn.):** *The Relationship of Pregnancies to the Surgical Treatment of Carcinoma of the Breast.* The breast carcinoma cases treated at the Mayo Clinic were divided into two groups, those which developed cancer during pregnancy and those in which pregnancy occurred after removal of a breast for cancer. There were 92 patients in whom a cancer of the breast developed during pregnancy, of whom 88 were traced. There were 55 patients in whom the breast had been removed for cancer and who subsequently became pregnant, all of whom were traced. Of the 92 cases in which a cancer of the breast developed during pregnancy, there were none in Grade I; 5.4 per cent were Grade II, 21.7 per cent Grade III, and 59.8 per cent Grade IV. Thirteen per cent were not graded. Of these 92 cases, there were 84.8 per cent with metastasis, of which none lived, and 15.2 per cent without metastasis. There were 55 cases operated upon which subsequently became pregnant. Whereas the pregnancy occurred from one to thirteen years after operation, most of them occurred between one to three years. There were 13 cases from between one and two years after operation, and 15 between two and three years. The grading of the tumors

in these cases was as follows: Type I, 4 cases; Type II, 8 cases; Type III, 15 cases; Type IV, 11 cases; and in 17 cases the tumor was not graded. Forty-five and five-tenths per cent had axillary metastasis, whereas, 54.5 per cent had none. The results obtained in this group were as follows: Of those surviving one or more years; there were 33 of 37; two or more years, 29 of 37; three or more years, 26 of 35; five or more years, 24 of 31; ten or more years, 12 of 18; and fifteen or more years, 7 of 12. Although these results seem to indicate that pregnancy occurring in a woman who has previously had a carcinoma of the breast does not offer as hopeless a prognosis as previously thought, it is Dr. Harrington's opinion that a woman who has had a carcinoma of the breast should be warned that she should not become pregnant.

**Dr. L. S. McKittrick (Boston) (Interstitial Irradiation in Breast Tumors)** began interstitial irradiation of breast tumors in 1913. His technique differed somewhat from that of Mr. Keynes in that the needles were placed between the breast and the muscle and also above the tumor in the breast. A gridiron method of introducing the needles was used. Almost immediately after the removal of the needle, the tumors began to decrease in size and the decrease frequently continued for four to five months. He has had 40 cases, 10 of which were operable, 20 inoperable, and 10 recurrent. There were 3 deaths. In the operable tumors there was complete regression of the tumor in 60 per cent. There was 50 per cent or more regression of the tumor in 12 per cent and less than 50 per cent regression in 28 per cent. He believes that the size of the tumor has a great deal to do with the ability of the radium to produce regression. Based on his results, he is of the opinion that in operable cancer of the breast irradiation is less desirable than surgery, because of the finding of viable cells in the irradiated mass in the large percentage of cases and because of the deformity and the pain following irradiation. He is also of the opinion that irradiation does not protect the axilla from invasion by the tumor.

**Dr. Carl Eggers (New York)** discussed **The Value of Radical Operation for Cancer in the Presence of Involved Lymph Nodes**. In the treatment of cancer the removal of the regional lymph nodes is of importance for cure. Involvement of the axilla in cancer of the breast should never keep one from doing a radical operation. In his mammary carcinomas, Eggers obtained five-year cures in 43.8 per cent, 33.3 per cent with axillary lymph nodes and 65.4 per cent without nodes.

**Dr. Rudolph Matas (New Orleans)** in discussing these papers emphasized that, although great advance has been made in the x-ray and radium treatment of cancer, at the present time these should be used merely as adjuncts and that the surgical removal of the tumor is most important. In closing the discussion, **Mr. Keynes** stated that for a number of years he had done routine biopsy and had observed no errors between the clinical diagnosis and that obtained histologically. Because, however, he obtained a recurrence in the skin wounds, he discontinued this procedure. At the present time he frequently removes either the tumor or the breast, and states that in no instance did he use irradiation in which the diagnosis was not definite either clinically or pathologically.

**Dr. Loyal Davis (Chicago)** discussed **The Results of Radiation on Gliomas of the Brain**. In considering the good effects obtained following x-ray treatment of brain tumors, frequently one has a false conception and does not take into consideration the results obtained from the operative removal of portions of the tumor and the decompression resulting from the operation. In the examination of cases previously operated upon and in which at the time tumor tissues were

breast has not been very satisfactory and because of this the author has resorted more and more as time has gone on to radium irradiation. He does not believe in Handley's conception of cell permeation but is of the opinion that cancer spreads entirely by lymphatic embolism. In 1922, he began using radium interstitial irradiation in cancer recurrences. In 1924, he began treating inoperable primary tumors of the breast. He treated 50 inoperable cases and at the end of eight years had 10 per cent of them living and well. He now treats earlier cases of cancer with interstitial radiation. He frequently removes the tumor or breast followed by irradiation but never does an axillary dissection. In those cases in which he examined the removed tumor nine months or more after the irradiation, he found that 50 per cent of the cases showed no remaining tumor cells. He felt because the other 50 per cent showed viable cells that the large bulk of the tumor had prevented complete destruction, and that in such instances when the tumor was large it was best to remove the tumor before irradiation. The radium needles are placed in the plane between the breast and the muscles, but from his experience he is convinced that removal of the axillary gland is unnecessary. It may actually do harm in those cases in which the glands are large and is unnecessary in those cases in which the glands are small or absent. He advocates local excision of the tumor when the tumor is small or when the diagnosis is uncertain to be followed by irradiation of the breast and axilla. If the tumor is large, simple removal of the breast without removal of the muscle followed by irradiation is done. The results obtained are about the same obtained from surgery because death is due to distant and not to local metastases. In all he has had 325 cases, 250 of which were followed from 1924 to 1934. There are 85 cases in which the disease was localized to the breast, of which 83.5 per cent were well after three years, and of which 71.4 per cent were well after four years. There were 91 cases in which the disease was localized in the breast and axilla, of which there were 51.2 per cent three-year cures and 29.3 per cent five-year cures. There were 74 cases which were definitely inoperable, of which there were 34.1 per cent three-year cures and 23.6 per cent five-year cures. As the axilla was not exposed in his cases, it is probable that in many of the cases in which he assumed there was no axillary involvement such actually had occurred, so that, correcting for this error, he believes that the three- and five-year cures should be 94.8 per cent and 86.3 per cent, respectively. Irradiation is much better than operation, because it is attended with a much lower mortality rate, and there is less danger of dissemination of the disease when it has once gotten in the axillary nodes.

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**Dr. William Jason Mixter (Boston): Rupture of the Lumbar Intervertebral Discs as a Cause for So-Called Sciatic Pain.** Frequently cases of low-back pain associated with sciatica are the result of rupture of the intervertebral disc and extrusion into the spinal canal. Sixty per cent of these come on immediately after injury, aggravated by bending and lifting, relieved by lying down, and there is frequently tipping toward the affected side. There is limitation of straight leg raising. There is also an absence of diminution of ankle reflex on the affected side. The x-rays occasionally show narrowing of the intervertebral disc, but this is seldom found. In cases of low-back pain associated with sciatica unrelieved by conservative orthopedic measures the patient should have a lumbar puncture. The puncture should be made in the fourth or fifth interspace. The first two drops of spinal fluid should be kept for examination, as the protein content of the spinal fluid is extremely important. The protein is normally from 40 to 50 mg. per cent; anything above that is abnormal and when present an intraspinal injection of lipiodol followed by roentgenography should be made to determine any encroachment upon the spinal canal. Five cubic centimeters of the lipiodol is introduced with the patient in the prone position on the fluoroscopic table and x-ray examination made in this position. The characteristic deformity shows encroachment upon the shadow produced by the lipiodol opposite the intervertebral disc. Mixter had 21 unoperated cases with negative lipiodol findings and 58 cases which were operated upon. In each instance there was a protrusion in the canal of the intervertebral disc. The operation which is done consists of a hemilaminectomy, usually removing the lamina involved and a portion of the lamina above and below. Occasionally it is necessary to resect the articular facet. The protrusion is removed, occasionally transdurally. Because of the back injury, and also because of the laminectomy, a fusion of the spine is usually done. In his cases a rupture occurred between the second and third lumbar in 1; between the third and fourth in 4; between the fourth and fifth in 35, or 60 per cent; between the fifth lumbar and first sacral in 17, or 30 per cent; and between the first and second sacral in 1. Of these patients 32 are well, 13 improved, 3 unimproved, 1 died of the operation, another died of urinary sepsis following the operation without any improvement, and 8 which have been observed from one to six months were too recent to evaluate. Seven have been operated upon with no evidence of rupture. There were 3 of these who had a localized arachnoiditis and the other findings were normal. The paper was discussed by **Dr. Kellogg Speed (Chicago)** who stated that he had had 100 patients with sciatica following trauma, and of this group 5 continued to have symptoms in spite of conservative orthopedic measures. Three of these were given a lipiodol injection and in all there were the characteristic deformities shown by Mixter. Speed advocates the use of simpler measures before resorting to lipiodol. **Dr. Howard Naffziger (San Francisco)** stated that many of these cases were previously operated upon for cord tumors. He has had 30 proved cases and states that many of these patients have repeated slight injuries, such as horseback riding or jumping. In many cases it is necessary to open the dura in order to determine the presence of a mass.

**Dr. Owen H. Wangensteen (Minneapolis)** presented **Studies on the Etiology of Acute Appendicitis.** The anatomy of the appendix was studied in over 800 specimens, and the Gerlach fold was found to be present in 80 per cent. In no instance was there any evidence of sphincter except in the fetus. The distensibility of the normal human appendix was 40 cm. of water; that of the appendix removed between attacks was 50 cm. of water; whereas that with acute suppurative appendicitis was 70 and above. In patients with appendicostomy it was found that similar pressures existed. In order to determine the bacterial influence in appendicitis, exudate from patients with acute suppurative appendicitis was introduced

removed and then subsequently irradiated, the author could find no correlation between the amount of deep x-ray treatment and the histologic change. Histologic examinations following irradiation of glioblastomas show more central necrosis and greater growth of collagenous tissues than in the untreated tissue, but there is apparently little inhibition of the growth of the tumor at the periphery. Clinically one is likely to be misled from results obtained from the irradiation.

In discussion Dr. Elliott Cutler (Boston) stated that irradiation definitely prolonged life in many of these patients, particularly in cases with medulloblastoma. These tumors are likely to recur, but by irradiation they have increased the survival rate from one year to six years in a number of cases.

Dr. F. L. Reichert (San Francisco) believes that x-ray is advantageous in treatment of these cases clinically. Recently they had been using heat applied directly to the brain substance by means of the high frequency current, which produces a destruction of tissues a considerable distance away from the site of application. In these cases, however, they are not using irradiation.

Mr. Julian Taylor (London) stated that although frequently there is little change in the histologic appearance of the tissue following irradiation, the clinical improvements are frequently very striking. For some time in those cases with a tumor on the left side of the brain in which he felt reasonably certain by a process of elimination the lesion was a glioma, he has employed only deep x-ray irradiation and has been very agreeably surprised at the improvement which these patients have obtained in that their choked discs and hemiplegia have disappeared.

Dr. W. E. Gallie (Toronto) in discussing *The Treatment of Fracture-Dislocation of the Cervical Spine* stated that they had been disappointed in the results obtained from reduction of cervical fractures because of too much danger of damage to the spinal cord. He advocates skeletal extension by means of ice tongs placed in the parietal bones. Whereas previously they used extension for a long time, recently they discontinued this because they observed cases with compression of the fifth cervical nerve. They now use very heavy traction for a period of minutes, following which they apply a head jacket cast, the whole procedure taking about an hour. Thirty to forty pounds of weight are applied for ten to twenty minutes and usually in this time satisfactory reduction is secured. This can frequently be facilitated by gentle manipulation. When the articular facets become locked, open reduction by levering the facets into place may be necessary or even resection of one of the facets. Reduction in fresh fracture is very much easier than in old ones. In the latter recurrence is likely to occur and because of this the author advocates spinal fusion according to the method of Hibbs which they have been using for four years.

Dr. F. J. Cotton (Boston) suggested the wiring together of the spinous processes instead of the fusion operation.

Dr. Frayer Gurd (Montreal) states that in Montreal they have been fusing the skull to the cervical spine by means of grafts from the ileum.

Dr. William Darrach (New York) discussed mild injuries of the cervical spine with unilateral subluxation. In nine years they have had 134 cases. These usually follow a mild injury, such as forcefully turning the head, sneezing, or some other trivial injury. The head is usually fixed in position and resembles torticollis. The diagnosis is made by means of stereoröntgenograms. In the milder cases reduction is secured by rest and gentle traction, using a gravity pull on an air mattress with the head in hyperextension. The head is then fixed in a plaster cast.

exposure of the joints to be arthrodesed. The amount of bone to be removed and its location are to be determined by carefully made preoperative x-rays.

**Dr. Isadore Zadek, New York City:** Dr. Zadek stated that acute osteomyelitis in the adult is very rare with no literature on the subject. He reported nine cases. "Acute" is rather a misleading word, since onset is slow and frequently follows earlier injury. Symptoms are localized pain with no fever or only slight rise in temperature. Leucocytosis is present only if there is fever. X-rays are negative for several weeks or months and then localized; irregular mottling of the bone is seen. Pathologically there is central granulation tissue and pus, more often in the shaft than in the end of the long bone, without subperiosteal involvement in most cases, the disease spreading along the medulla. Sequestrum formation is rare. Treatment is operative and consists of decompression by removal of small window of bone over diseased area.

**Dr. R. E. Robertson, Toronto,** reviewed treatment of acute staphylococcal osteomyelitis as a clinical entity in the light of recent serologic findings. Clinical experiments and observations showed titer could be raised five to fourteen times by use of toxoid; this should be used as a preventive measure in children with staphylococcal skin infections, etc. Acute cases of infection must not receive toxoid until later, however. Operative treatment should be used only in those cases of osteomyelitis with abscess present, as there is no indication otherwise. Titer must be raised before operating a Brodies abscess, especially in elderly individuals.

In discussion, **Dr. H. Winnet Orr, Lincoln, Neb.,** showed several excellent results in osteomyelitis treated by his method with vaseline packs and immobilization in plaster.

**Professor Lelio Zeno, Rosario de Santa Fe, Argentine,** discussed his treatment of burns and showed moving pictures of the method. Burns, like fractures, are a condition and not a disease and are benefited by immediate immobilization in plaster of Paris in both children and adults. Pain is suppressed almost instantly and infection prevented. Plasters wet with cold water are applied directly to burned areas with limbs in good position after evacuating blisters if they are very large or tense. These plasters are not changed for at least ten days in first and second degree burns. Leg plasters are supported on Braun splints and arms are suspended from overhead frame. Bed clothes are supported by cradles to allow free ventilation.

**Dr. Leo Mayer, New York City,** stated his opinion that the secret of proper treatment in slipping of the femoral epiphysis is early diagnosis. Such diagnosis should be made on a history of slight limp with limitation of internal rotation and on radiographs showing loss of normal bulge of head superiorly, prominence of superior lip of neck at epiphyseal line, and apparent diminution in the length of the epiphysis. Treatment: drilling of epiphyseal line through trochanter in seven or eight places with plaster of Paris immobilization for two to three months.

**Symposium—Fractures of the Neck of the Femur:** **Dr. Guy W. Leadbetter, Washington, D. C.,** stated that fifty-nine cases followed showed 71 per cent union with an additional 6 per cent good functional results without union by nonoperative treatment. Conservative treatment should be applied when possible and should be the method used in teaching although internal fixation is more adequate. A recent series shows 75 per cent operative and 25 per cent conservative. Use of heel-palm test for reduction was emphasized.



into the appendix exposed in appendicostomy and in no instance did an infection occur. The appendix of a patient with an appendicostomy was cannulated and it was found that from 1 c.c. to 2 c.c. were secreted in twenty-four hours. In investigating a large number of animals, it was found that the rabbit's appendix was similar to that of a human. It secretes 0.02 c.c. per minute and if the base of it is tied it will perforate in from ten to fourteen hours. If erotin oil is given by mouth or hypertonic solution intravenously, the perforation occurs much earlier, in from three to six hours. These effects do not occur if the arteries of the appendix are blocked. The volumetric content of the human appendix is from 0.1 to 0.2 c.c.

Dr. E. P. Lehman (University, Va.) discussed *The Place of Exploratory Operation in the Surgery of Subphrenic Abscess*. He has had 9 cases of subphrenic abscess which were explored and no abscess found. There were 20 cases in which an abscess was found, giving a correct diagnosis of 51.7 per cent. Five cases which were missed clinically were found at autopsy or in some other way. In the cases operated upon in which abscesses were found, there is a mortality rate of 23 per cent. Aspiration is condemned as a diagnostic procedure, because it is dangerous and also unreliable. The mortality rate in the cases which were explored and the abscess not found was 55.5 per cent. All of these, however, died of other conditions: 2 of multiple liver abscesses, 1 of empyema, 1 of a pulmonary embolism, and 1 of an undetermined sepsis. The extraserous approach is perfectly safe and exploratory operation is justified if a diagnosis cannot be made otherwise.

In discussion, Dr. Alton Ochsner (New Orleans) emphasized the importance of early diagnosis and exploration if diagnosis cannot be made and emphasized the importance of the extraserous approach because of its relative safety and lower mortality.

Dr. Howard Lillenthal (New York) advised, in these cases in which the diagnosis is difficult, the production of a pneumoperitoneum before the taking of an x-ray. Dr. Edwin Beer (New York) suggested in those cases in which there is a difficulty of diagnosis that a perirenal insufflation of air or carbon dioxide be made.

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## REVIEW OF THE FIFTIETH ANNIVERSARY MEETING OF THE AMERICAN ORTHOPAEDIC ASSOCIATION, LINCOLN AND OMAHA, NEB., JUNE 2 TO 4, 1937

WALLACE H. COLE, M.D., ST. PAUL, MINN.

*(From the Division of Orthopaedics of the Department of Surgery, University of Minnesota Medical School)*

THE Fiftieth Anniversary meeting of the American Orthopaedic Association was held in Lincoln and Omaha, Neb., June second to fourth of this year. The major contributions were:

Dr. R. Plato Schwartz, Rochester, N. Y., outlined the requirements for a subastragalar arthrodesis and advocated a lateral J-shaped incision for complete

exposure of the joints to be arthrodesed. The amount of bone to be removed and its location are to be determined by carefully made preoperative x-rays.

**Dr. Isadore Zadek, New York City:** Dr. Zadek stated that acute osteomyelitis in the adult is very rare with no literature on the subject. He reported nine cases. "Acute" is rather a misleading word, since onset is slow and frequently follows earlier injury. Symptoms are localized pain with no fever or only slight rise in temperature. Leucocytosis is present only if there is fever. X-rays are negative for several weeks or months and then localized; irregular mottling of the bone is seen. Pathologically there is central granulation tissue and pus, more often in the shaft than in the end of the long bone, without subperiosteal involvement in most cases, the disease spreading along the medulla. Sequestrum formation is rare. Treatment is operative and consists of decompression by removal of small window of bone over diseased area.

**Dr. R. E. Robertson, Toronto,** reviewed treatment of acute staphylococci osteomyelitis as a clinical entity in the light of recent serologic findings. Clinical experiments and observations showed titer could be raised five to fourteen times by use of toxoid; this should be used as a preventive measure in children with staphylococcal skin infections, etc. Acute cases of infection must not receive toxoid until later, however. Operative treatment should be used only in those cases of osteomyelitis with abscess present, as there is no indication otherwise. Titer must be raised before operating a Brodie's abscess, especially in elderly individuals.

In discussion, **Dr. H. Winnet Orr, Lincoln, Neb.,** showed several excellent results in osteomyelitis treated by his method with vaseline packs and immobilization in plaster.

**Professor Lelio Zeno, Rosario de Santa Fe, Argentine,** discussed his treatment of burns and showed moving pictures of the method. Burns, like fractures, are a condition and not a disease and are benefited by immediate immobilization in plaster of Paris in both children and adults. Pain is suppressed almost instantly and infection prevented. Plasters wet with cold water are applied directly to burned areas with limbs in good position after evacuating blisters if they are very large or tense. These plasters are not changed for at least ten days in first and second degree burns. Leg plasters are supported on Braun splints and arms are suspended from overhead frame. Bed clothes are supported by cradles to allow free ventilation.

**Dr. Leo Mayer, New York City,** stated his opinion that the secret of proper treatment in slipping of the femoral epiphysis is early diagnosis. Such diagnosis should be made on a history of slight limp with limitation of internal rotation and on radiographs showing loss of normal bulge of head superiorly, prominence of superior lip of neck at epiphyseal line, and apparent diminution in the length of the epiphysis. Treatment: drilling of epiphyseal line through trochanter in seven or eight places with plaster of Paris immobilization for two to three months.

**Symposium—Fractures of the Neck of the Femur:** **Dr. Guy W. Leadbetter, Washington, D. C.,** stated that fifty-nine cases followed showed 71 per cent union with an additional 6 per cent good functional results without union by nonoperative treatment. Conservative treatment should be applied when possible and should be the method used in teaching although internal fixation is more adequate. A recent series shows 75 per cent operative and 25 per cent conservative. Use of heel-palm test for reduction was emphasized.

Dr. R. T. Harris, Toronto, pointed out that internal fixation has been used for three years at the Toronto General Hospital. The Smith-Peterson nail is used, and he feels that "unsolved fracture" is nearly conquered. The principles of treatment are: (1) accurate reduction; (2) close approximation of fragments; and (3) maintenance of approximation. Failures are due to: (1) nail in poor position; (2) too early weight bearing, eight weeks being minimum time.

Dr. W. W. Plummer, Buffalo, uses Smith-Peterson nail with elaborate technique and a frame that clamps to table. He feels pain is relieved early and the fear of long fixation in plaster of Paris is eliminated.

Dr. E. G. Brackett, Boston, in discussing reconstruction operations for ununited fractures of the neck of the femur, divided methods into two groups: (1) where articular structures remain intact and can be used (Brackett); (2) where non-articular structures are used. Procedure must be chosen on basis of what will stand up to expected use.

Discussion of the symposium showed the Smith-Peterson nail to be the most popular method of internal fixation. Orr felt that there was a tendency to minimize dangers of operation and demonstrated cases treated with moleskia traction and double leg plaster with excellent results. Henderson advocated use of lag-screw and showed slides of perfect results. Albee showed advantages of his reconstruction operation from viewpoint of comparative anatomy with the advantage of long abductor lever. Dickson said the Brackett operation was the best of all reconstruction operations but that fixation must be used for three to five months.

Dr. Robert Funsten, Charlottesville, Va., reported twenty cases of so-called "dash-board" dislocations of the hip occurring in passengers in the front seat of an automobile with head-on collisions and due to force exerted on flexed and adducted femur. Treatment: immediate reduction with traction or plaster for six to eight weeks; no weight bearing for three months. Prognosis good in uncomplicated dislocation, but with fracture of posterior lip of acetabulum some disability remains.

Mr. R. Watson Jones, Liverpool, England, spoke by invitation, on the development of fracture treatment in Great Britain. General standards have been low, but fracture clinics are being started so that now about one-fourth of the cases are treated by experts. The basis of the new development is a threefold program: (1) establishment of fracture units in the hospitals; (2) better teaching of the medical students and postgraduates; (3) the formation of a network of industrial rehabilitation centers which consider both the physical and mental side of the problem. "Malingers are made and not born." A motion picture film to show old and new methods of fracture treatment is used as an educational method. This was exhibited.

Dr. Svante Orell, Stockholm, Sweden, described three types of bone used for surgical bone grafting which complement but do not supplant live autogenous grafts: (1) "Os purum," bone which has been cleaned of cellular elements by treatment in salt solution, potassium hydroxide, and acetone, and which is used to fill in gaps after resection, since it can be cut to exact shape and since its porous nature allows osseous and connective tissue cells to penetrate easily. (2) "Os novum," new bone formed on and in a piece of os purum, transplanted sub-

periosteally on the tibia and removed in one to two months. Used for spine fusions and pseudarthrosis. (3) "Boiled bone," osteomyelitic or sarcomatous bone boiled and immediately replaced to fill gap left by its removal.

Dr. Paul Swett, Hartford, Conn., spoke on synovectomy used to preserve joint surfaces and to remove disease synovial membrane. It is indicated in: (1) certain cases of atrophic arthritis; (2) chronic traumatic arthritis; (3) benign tumors of synovial membrane; (4) syphilitic arthritis; (5) intermittent hydrops; (6) chronic ossifying synovitis. It is not indicated in hypertrophic or tuberculous arthritis.

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## SIXTY-THIRD ANNUAL MEETING OF THE AMERICAN NEUROLOGICAL ASSOCIATION, ATLANTIC CITY, JUNE 3 TO 5, 1937

WILDER PENFIELD, M.D., AND JOSEPH EVANS, M.D., MONTREAL, QUEBEC

WHAT is the limit of tolerance of the brain for radiotherapy? This question was answered in part by Percival Bailey, J. O'Connell, and A. Brunschwig in a paper entitled *Experiences with the Roentgen Treatment of Cerebral Gliomas*. The authors described the results of treatment of two cases of glioblastoma and one of medulloblastoma. The first two patients received 1,500 r. units and 1,800 r. units; the third, a child, received 1,300 r. units, in divided doses. The dosage was great enough to produce a weeping edema of the scalp. Subsequent to treatment all signs of tumor disappeared, but at the end of about eighteen months all three patients became progressively weak and asthenic until death occurred.

Postmortem histologic study of the brains showed no sign of tumor remaining, but it also showed extensive damage to neurones. There was loss of Nissl substance in ganglion cells, appearance of intracellular fat, and fragmentation of neurofibrillae. The glial cells were also markedly affected: swelling of oligodendroglia, elastotodendrosis of astrocytes, hypertrophy of microglia, and active phagocytosis within the brain. The meninges and blood vessels of the brain showed little change. The pituitary body was unaltered.

The authors believe that since such a highly destructive effect can be achieved through the intact skull, there is no indication for direct roentgen treatment of brain tumors through a craniotomy opening at operation as practised in the neurosurgical clinics of Sachs and of Elsberg.

The consensus of opinion among the discussors was that somewhere a middle ground will be found so that neoplastic cells may be destroyed and cerebral tissue preserved. To achieve such a therapeutic effect is, of course, the ambition of all radiotherapists. The upper limit of x-ray dosage at least is clearly described by the authors.

Pect and List reported a study of facial sweating in patients who had been submitted to varying types of sympathetic and trigeminal neurotomy. Although after sympathectomy sweating in the face disappears when the patient is hot, there occurs increased sweating as the result of gustatory-salivary reflex. This reflex produces sweating in the face when sour substances are taken into the mouth.

Hyperactivity of the sweat glands was found also after sympathectomy when acetylcholine was injected. This suggests that sweating, which is to be listed as a parasympathetic activity, has a peripheral apparatus which is hypersensitized to humoral stimulation by section of its nerve connection with the central nervous system. This finding is in conformity with the discovery by James White and his coworkers that postganglionic sympathectomy hypersensitizes the peripheral blood vessels to the activity of adrenalin circulating in the blood.

Thus it may be assumed that section of the autonomic outflow from the cord cuts the parasympathetic fibers to the sweat glands in the face and sympathetic fibers to the vessels producing sensitization of each to its own particular humoral stimulant. This is another example of the activation of the autonomic function by humoral as well as neural stimulation.

Sachs, Schwartz, and Weddell presented evidence that taste fibers from the anterior two-thirds of the tongue sometimes traveled to the facial nerve by way of the greater superficial petrosal nerve, instead of invariably through the chorda tympani to the facial nerve as ordinarily believed. The evidence was derived from the study of patients with section of the chorda tympani during radical mastoidectomy as compared with the results of section of the greater superficial petrosal during trigeminal rhizotomy.

Penfield and Boldrey made an analysis of the motor and somatic sensory representation in the cerebral cortex of man from evidence obtained during stimulation of the cortex in a search for epileptogenic foci.

Schwab and Tureen pointed out that the spinal cord might recover after fifteen minutes of ischemia but that longer periods of arrest of circulation were invariably fatal to the cord. The anterior horn cells were more vulnerable than other neurones.

There is a frequently recurring tendency to make elaborate laboratory or mathematical studies replace simple clinical thinking. A typical example of this tendency was a paper by Savitsky and Kessler urging the adoption of the Ayala index in cerebrospinal fluid studies. By comparing the spinal fluid pressure before and after withdrawal of 10 c.c. of fluid, the index expresses mathematically the fact that the withdrawal has been made from a larger or smaller total volume of fluid. The use of the Ayala index substitutes a figure for simple thinking. But one is forced to ask, why clothe a mathematical formula with authority?

Wolff and Graham in a communication, summarized but not read, concluded from a study of certain cases of migraine that the pain may be relieved by ergotamine tartrate because this drug causes constriction of the cranial (not the cerebral) arteries. They pointed out also that the pain might be stopped by shutting off the temporal or the external carotid arteries and that distention of the temporal artery by saline at operation produced the pain. The conclusion might seem to be that if relief from ergotamine proved to be too transient, surgical arterial ligation might be undertaken, but the authors did not offer this conclusion.

The session was opened by a scholarly symposium on electrical studies of fundamental nervous processes by the neurophysiologists Bronk, Gasser, Lorente de No, and Bishop. The electrical phenomena described in neurone and synapse

are of interest, but the time for the application of this new knowledge to clinical neurology or neurosurgery has not yet come. It may therefore be ignored in a report such as this. For the same reason the majority of the papers presented have not been discussed here. Selection of a few papers for this report has been made on the basis of what seemed to have surgical application, although the element of personal interest and the recurring lure of Atlantic City's ocean breeze may also have determined the selection to some extent.

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## REVIEW OF THE THIRTEENTH SCIENTIFIC MEETINGS OF THE AMERICAN HEART ASSOCIATION

FREDERICK R. MAUTZ, M.D., CLEVELAND, OHIO

The American Heart Association held its thirteenth scientific meetings in Atlantic City, N. J., on June 7 and 8, 1937. Following are abstracts of the subjects of particular interest to the surgeon:

**Observations on Phlebitis, Dr. Edward A. Edwards, Boston:** Experimental observations were presented demonstrating how complete venous thrombosis causes thickening and distortion of the valves. Incomplete thrombosis is especially likely to occur at the valve sites. The result is that the originally thin and flexible valves are converted into thick, inelastic structures with associated functional disturbances of stenosis and regurgitation. It was pointed out that in clinically recognizable phlebitis relatively early exercise is not dangerous and that excessive immobility of the affected part may lead to a "stagnation clot" above the zone of phlebitis; and since this clot may not be as firmly attached to the vein wall as the thrombus in the zone of more severe inflammation, there may be greater danger of pulmonary embolism. If pulmonary infarction occurs, ligation of the main venous trunk above the site of the phlebitis was advised. In varicose phlebitis ligation of the main venous trunk plus small injections of sclerosing agents was advised.

In the discussion Dr. Alton Ochsner, New Orleans, referred to Dr. Baneroff's recent work showing that about 12 per cent of postoperative patients show an increasing clotting tendency with evidence that low protein high carbohydrate diet plus intravenous sodium thiosulphate reduces the clotting tendency. Dr. Ochsner advocated the use of leeches in phlebitis. He stated that they shorten convalescence, the probable mechanism being by the local and systemic action of hirudin. It was also pointed out that intravenous heparin has been recommended postoperatively to eliminate postoperative thrombosis and embolism.

**The Treatment of Scleroderma by Meecholy Iontophoresis, Dr. A. Wilbur Duryee and Dr. Irving S. Wright, New York City:** Thirty-four cases diagnosed as scleroderma were included in the series. There were 8 males, 26 females. The average age was 37.5 years. In 32 there was a definite Raynaud's syndrome. The treatment consisted of the local application of meecholy in asbestos dressings over the affected parts and the passage of an electric current of 20 ma. between a positive electrode placed over the dressing and a negative electrode

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The results of acute arterial occlusion depend upon the amount of available collateral circulation. Peripheral angiospasm was believed to develop and reduce the amount of collateral blood supply. The importance of medical treatment during the first 24 hours was emphasized. This consisted of local warmth, care being taken not to cause burns, whiskey, intravenous papaverine hydrochloride as a vasodilator, and intravenous sodium thiosulphate as anticoagulant. Early therapy of pressure and suction is believed to be of value if a pink color can be maintained; late treatment may be dangerous if indications for amputations are not recognized. In cases which recover with this type of treatment, "ischemic neuritis" may be very disabling. Conservative treatment does not restore as good a circulation as successful embolectomy, but the satisfactory results following embolectomy were not believed to be striking enough to warrant the frequent employment of this procedure.

**Hypertension Produced by Constriction of the Renal Artery in Sympathectomized Dogs, Dr. Norman E. Freeman, Philadelphia, and Dr. Irvine H. Page, New York City:** In a series of six dogs, three-stage thoracoabdominal sympathectomy was done preliminary to producing renal ischemia by the Goldblatt method. Hypertension resulted in every experiment in spite of the sympathectomy. One animal was found with spontaneous hypertension. In this animal sympathectomy caused a fall in mean arterial pressure; later, renal ischemia was produced and hypertension resulted. In a second series of four animals, cardiac denervation was done in two stages previous to producing renal ischemia and again the hypertension developed after production of renal ischemia, indicating that reflex control of the cardiac output played no rôle in the hypertension. It was also believed that there was no increased adrenalin secretion. Blood volume determinations on normal and hypertensive dogs showed no difference. It was pointed out that complete proof that the sympathetic nervous system played a part would require that the outlying ganglia be removed in addition to the main trunks and ganglia.

In the discussion Dr. Harry Goldblatt pointed out that the studies in experimental hypertension do not completely rule out the possibility that sympathectomy may lead to improvement in human cases. The early phenomena may be of a reversible nature, which cannot be the case in renal ischemia produced by a silver clamp.

**The Physiologic Effects of Extensive Sympathectomy for Essential Hypertension, Dr. Edgar Van N. Allen and Dr. A. W. Adson, Rochester, Minn.:** In cases of essential hypertension believed to be of vasomotor origin but resistant to medical treatment, these authors have been doing bilateral two-stage thoracolumbar sympathectomy, plus removal of adrenal tissue in some cases. Patients were selected on basis of response to (1) vasodilators, (2) chilling extremities, (3) sodium penicillin, (4) rest and sleep. The following postoperative effects were noted: (1) fall in blood pressure, (2) orthostatic tachycardia which gradually disappeared in time, (3) diminution in response to cold test in favorable cases, (4) diminished sweating of lower torso and legs, (5) postural changes in blood pressure, (6) slight lowering of basal metabolic rate, (7) improvement in renal function and eyegrounds in some cases, (8) no impaired motor function, (9) mild diarrhea in a few cases, (10) relief from dysmenorrhea. Forty-five patients were operated on from January, 1935, to February, 1937. Of these there were no operative fatalities. The present status is: 20 failures, 12 fair results from 3 to 18 months, 11 good results from 3 to 23 months.



placed over the back. Treatments for 20 to 30 minutes were given two to three times per week. Local hyperemia persists 4 to 5 hours after treatment, indicating local absorption.

There was definite improvement in symptoms, greater degree of motion of fingers, and definite softening of the skin. Fifty treatments were considered adequate to produce a maximum degree of improvement, but improvement was seen with fewer treatments. Of 27 cases considered to have been adequately treated, 16 showed definite improvement and 11 showed slight or no improvement. These results were believed to be better than those following sympathectomy or parathyroidectomy. There was no evidence of coronary artery sclerosis following the use of mechoyl. Intravenous or subcutaneous administration was believed to be dangerous. Of the group treated, there was one case of skin hypersensitivity to mechoyl.

In the discussion Dr. Edward V. Allen said that the results of this report are more encouraging than the results of operation. He also pointed out the development of coronary artery sclerosis in animals by the administration of mechoyl.

**The Pathologic Basis for Intermittent Claudication in Arteriosclerosis, Dr. J. Ross Veal, New Orleans:** Forty-one cases of arteriosclerosis with intermittent claudication were studied by the method of vasography. These patients complained of bilateral pain in calf muscles after walking one to two blocks and they obtained relief after 1.5 to 15 minutes' rest. The average age of the group was 51.4 years. The arteriography was done with the patient at a basal state.

In comparing the results of this study with the normal arteriogram, three groups were recognized: Group 1—21 cases showed complete obstruction of one or more main arterial trunks. Group 2—6 cases showed narrowing but not complete obstruction of main arteries. Group 3—14 cases showed large arteries to be patent and of normal size with defects in the small muscular branches. All the patients showed failure of visualization of the small muscular branches and their arborization as seen in normal cases.

There was no direct correlation between the size of the artery occluded and symptoms. The most marked symptoms were present when abundant collateral channels failed to appear.

Symptoms were believed to be due to relative ischemia, depletion of the nutrient substances in the tissue fluids, and acute starvation of the muscle following activity. Oxygen studies showed no decrease in the oxygen saturation of the arterial blood during exercise. The possibility of a metabolic pain factor, as suggested by Lewis, was believed logical.

**Experiences With the Conservative Management of Acute Arterial Occlusion, Dr. Louis G. Herrmann, Cincinnati:** The report dealt with 53 cases of acute arterial occlusion, 44 thromboembolic and 9 ligations. No cases of aneurysm or Buerger's disease were included. It was pointed out that an accurate differential diagnosis between thrombosis and embolism was sometimes difficult. The importance of early diagnosis and early institution of therapy was emphasized. Pain was an early symptom in only 50 per cent of the cases; numbness, coldness, and paresthesia were other early signs. Absent pulse, lowered skin temperature, pallor, sensory disturbances, and impairment of function characterized the extremity following acute arterial occlusion.

The results of acute arterial occlusion depend upon the amount of available collateral circulation. Peripheral angiospasm was believed to develop and reduce the amount of collateral blood supply. The importance of medical treatment during the first 24 hours was emphasized. This consisted of local warmth, care being taken not to cause burns, whiskey, intravenous papaverine hydrochloride as a vasodilator, and intravenous sodium thiosulphate as anticoagulant. Early therapy of pressure and suction is believed to be of value if a pink color can be maintained; late treatment may be dangerous if indications for amputations are not recognized. In cases which recover with this type of treatment, "ischemic neuritis" may be very disabling. Conservative treatment does not restore as good a circulation as successful embolectomy, but the satisfactory results following embolectomy were not believed to be striking enough to warrant the frequent employment of this procedure.

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Some Problems in the Diagnosis, Prognosis, and Treatment of Acute Arterial Occlusion, Dr. Harold E. Rykert and Dr. Duncan Graham, Toronto: In the diagnosis, two types of pain were recognized: (1) Early severe sharp pain at the level of the arterial occlusion believed to be due to arterial spasm at the site of embolic occlusion. This type of pain is absent in thrombosis. (2) Later dull pain distal to the point of arterial occlusion due to ischemia. Spasm was believed also to affect collaterals. In 10 consecutive cases of occlusion of main arteries of the lower extremity, 5 responded to conservative treatment, and in 5 cases this treatment was ineffectual. There was spontaneous recovery in 7 out of 12 cases involving the upper extremity. Conclusions: (1) Primary disease is most important factor in determining the outcome. (2) Early treatment with pressure-suction and antispasmodics and heat to the body is of value. (3) Embolectomy is rarely indicated.

The Diagnosis and Treatment of Chronic Constrictive Pericarditis, Dr. Paul D. White, Boston. Dr. White introduced a patient, O. W. P., a physicist who had suffered from the disease. Mr. P. described his symptoms, characteristic of chronic cardiac compression, and said that he was much improved following the decompression operation, which was performed by Dr. Churchill.

Acute and Chronic Compression of the Heart, Dr. Claude S. Beck, Cleveland: The pathologic physiology of cardiac compression, acute and chronic, was demonstrated by motion pictures. The rise in venous pressure and fall in mean arterial pressure, diminution of pulse pressure with compression of the heart by pericardial hemorrhage, purulent pericarditis, pericardial effusion, pericardial and epicardial scar, localized or generalized, or combinations of the above, the enlargement of the liver, formation of ascites, hydrothorax with marked rise in venous pressure, as high as 42 cm. of water in the chronic form of cardiac compression were demonstrated. The operative technique was shown in two cases. A group of several patients were shown preoperatively and postoperatively, all with marked improvement. It was pointed out that the heart never hypertrophies and that it may undergo "disuse atrophy" as a result of chronic compression. Two triads were discussed. The triad for acute compression consists of (1) high venous pressure, (2) low arterial pressure, and (3) small quiet heart. The triad for chronic compression consists of (1) high venous pressure in the arm, (2) ascites, and (3) small quiet heart.

## REPORT OF PROCEEDINGS OF THE AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS, JUNE 14, 15, AND 16, 1937

CLYDE DEMING, M.D., NEW HAVEN, CONN.

*(From the Division of Urology of the Department of Surgery, Yale University  
School of Medicine)*

Tumors of the Adrenal Cortex, Dr. A. J. Scholl, Los Angeles: This was an excellent paper, giving the experience with two cases of adrenal tumors which were diagnosed by air injection and palpable masses. The patients were operated upon. One died in thirty-six hours of extremely low blood pressure although she had had extensive treatment by intravenous methods of calcium chloride.

Autopsy showed an absence of the adrenal on the other side. The other patient lived longer, but the cause of death was the same. Interesting exposure of the adrenal tumor was made by placing the patient in the procumbent position with a depressed head and flexion of the trunk at the hips. The special point at issue was the likelihood of the absence of one adrenal.

**Squamous Cell Carcinoma of the Kidney Pelvis, Dr. Charles C. Higgins, Cleveland:** Sixty-five cases are now reported. The causes are leucoplakia, chronic inflammation, and deficiency in vitamin A. Males and females are equally involved. The urinary symptoms were those of frequency of urination, pain in the back, dysuria in 70 per cent, and general malaise over some period of time. The prognosis is grave. No case lived longer than five years.

**Three Unusual Primary Malignant Tumors of the Kidney, Dr. Frank S. Patch, Montreal:** Unusual malignant tumors of the kidney are reported.

**Tumors of the Renal Pelvis and Ureter, Dr. John R. Caulk, St. Louis:** Tumors of the renal pelvis and ureter form 5 to 10 per cent of all renal tumors. Eighty per cent of tumors of the renal pelvis are papillary; 60 per cent invade the kidney pelvis and ureter. Transplants do not take place unless there is a break in the mucous membrane. The disease is probably a generalized one of the mucous membrane. Treatment should include excision of the ureter as well as the kidney.

**Dr. MacKenzie** reported an unusual case of neurocytoma of the kidney in which massage of the left adrenal caused no change in blood pressure, but massage of the right adrenal raised the blood pressure one hundred points. Fifty cases are reported in the literature.

**Dr. Cahill** discussed the paper, reporting one hundred cases of air injection of the perirenal tissues without accident. Only one-fourth of the cases may be diagnosed by this method. Patients with suprarenal tumors have both male and female hormones in the urine. The female may show fifteen times as much male hormone in the urine as is shown in the normal male urine. Some may not have any female or male hormone.

**Supernumerary Kidney, Dr. Joseph F. Geisinger, Richmond:** Dr. Geisinger reports two cases of supernumerary kidney from autopsy. Thirty-eight cases are reported. The small kidney was found above and medial to the normal kidney, the supernumerary kidney having its own blood supply and ureter.

**Clinical and Radiologic Data With Congenital and Acquired Single Kidney, Dr. William F. Braasch and Dr. J. W. Merrieks, Rochester, Minn. (by invitation):** Sixty-eight cases of congenital and acquired single kidney are reported. The male and female are equal in number. A congenital, solitary kidney shows asymmetry to the trigone. The right is more frequently absent than the left. The psoas muscle is less distinct and wider in adenesia (absence of one kidney). The outline of the solitary kidney is larger than normal; its pelvis is larger; its function is faster with intravenous test. Scoliosis is present in the direction of the absent side.

**The Problem of the Solitary Diseased Kidney, Dr. William E. Lower, Cleveland:** Dr. Lower stressed conservatism in the treatment of diseases of a single kidney, especially advising drainage of the kidney during the acute phases of infection or after the removal of calculus.

**The Ectopic Kidney.** Surgical Aspects in a Series of Ectopic Kidneys, Dr. David W. MacKenzie and Dr. Allen B. Hawthorne, Montreal (by invitation): A review of the literature was made, giving the various types of ectopic kidneys: unilateral, bilateral, and crossed ectopic kidneys. Male and female are equally involved. Treatment depends upon the pathology.

**A Further Report on the Relationship of Papillary Lesions to Renal Calculus,** Dr. Alexander Randall, Philadelphia: Bases for stone formation: (1) Begin on papilla; (2) have attachment to papilla; (3) originate in minor calix; (4) initiatory lesion found; (5) initiatory lesion found in papilla; (6) deposit of calcium within the distal tubules; (7) calcium plaque observed at autopsies; (8) forty-one of such examples found; (9) calcium plaque found chemically to yield calcium and nucleate; (10) pure calcium phosphate and oxalate occur on the basement membrane of the tubules; in 609 autopsies calcium plaques were found in 2.9 per cent.

Experimental work: Avitaminosis in rats gives ulcer of the papilla. Rabbits' kidneys secrete and concentrate toxins injected into the blood stream. The distal tubules are most greatly involved in this toxic experiment. Parathyroid hormone injection in dog has given one calcium plaque on the papilla.

Impression to date with regard to stone formation is that there must be an initiatory ulcerative lesion on which forms a calcium plaque.

**Spontaneous Reno-Intestinal Fistula.** Report of Two Cases, Dr. Miley B. Wesson, San Francisco: Two cases reported; one case operated upon died; second case not operated upon. Both probably had perirenal abscesses.

**Roentgenological Examination of the Kidney With Special Reference to Injuries Associated With Retrograde Pyelography,** Dr. William E. Stevens, San Francisco: Dr. Stevens demonstrated that it is difficult to pass a catheter or bougie through a normal ureteral or kidney pelvic wall. If these structures are penetrated by ureteral instruments, the wall is usually pathologic.

**Malignancy of the Bladder Occurring in a Hunner Ulcer,** Dr. Francis B. Hagner, Washington, D. C.: Malignancy of bladder occurring in a Hunner ulcer eleven years after initiatory lesions proved by histologic sections; recovery.

**Experiences With High Voltage Deep Therapy in the Treatment of Malignant Tumors of the Urinary Bladder,** Dr. Roger C. Graves and Dr. Richard Dresser, Boston (by invitation): The use of high voltage machines 200 K.V. for carcinoma of the bladder has given gross evidence of regression of the tumor. Sixteen to eighteen hundred units given. Twenty-four cases treated. Supervoltage treatment gives but few cures. Combined treatment with surgery is advised.

**Radio Therapy of Bladder Carcinoma: Five-Year Results—Failures—Future Therapy,** Dr. Benjamin S. Barringer, New York City: Surgery gives 25 per cent five-year cures; radiation, 34 per cent five-year cures. However, serious complications due to infections of the kidneys occur. The treatment with 800 to 1,000 K.V. is discouraging. Supervoltage treatment gives somewhat deeper penetration and more regression of the tumor but not necessarily more cures.

**A Report After Ten Years of a Series of Bladder Tumors Treated by Suprapubic Radon Implantation,** Dr. Edward L. Keyes, New York City: Thirty-one cases reported. One postoperative death. Recurrences controlled by radon seeds. Ten of the thirty-one cases were tumors of Grades I and II.

**Successful Radical Perineal Resection of the Bladder Neck for Carcinoma, Dr. Clyde L. Deming, New Haven, Conn.:** Hugh Young's radical operation for carcinoma of the prostate applied to bladder neck cancer with a six-year cure with full control of urination and a normal bladder capacity. A new procedure.

**Methods of Selecting the Proper Operative Treatment for Cancer of the Bladder, Dr. Hugh Cabot and Dr. John M. Pae, Rochester (by invitation):** Methods used for this work were cystograms, pyelograms, and biopsies. Errors in diagnosis lay within the field of faulty estimation of the position of the tumor and its extension and lack of full appreciation of the renal complications.

**Human Prostatic Infection With *Brucella Abortus* (*Alcaligenes Abortus*), Dr. Montague L. Boyd, Atlanta, Ga.:** Report of a case of human prostatic infection with *Brucella abortus* proved by culture.

**Modern Plastic Perineal Prostatectomy—Its Indications and Advantages, Dr. Frank Hinman, San Francisco:** Dr. Hinman reported twenty-five cases with completely closed perineum, after fully controlling the hemorrhage at the bladder neck by closing the prostatic cavity. He now, however, uses a wick drainage in the perineum rather than tight closure of the skin. This wick drain prevents abscess formation in the operative field. Care must be taken to obtain complete hemostasis. Average postoperative period is sixteen days for twenty-five cases. The technique presented with slides and movies. The advantage of perineal prostatectomy is the removal of carcinoma originating within the hypertrophy, which occurs in 10 to 14 per cent of the cases.

**Prostates in Women, Dr. Hugh H. Young, Baltimore:** Dr. Young reported three cases of supposed females who were, in actual fact, proved to have prostatic tissue around the urethra, although they were pseudohermaphrodites, who had external genitalia of the female and an ovary on one side and a testis on the other.

**Prostigmin in the Treatment of Ureteral Calculi, Dr. Benjamin H. Hager, Los Angeles:** Read by title. Discussion by Dr. O'Crowley, who stated that a drug allied to prostigmin called "No. 568" made by Sharp and Dohme acts better than prostigmin. Two cubic centimeters of this drug given intramuscularly has given remarkable results in seventeen cases. The drug must be given intramuscularly and the areas must be massaged for three or four minutes, as it causes a little smarting. This, however, is not significant.

**Plastic Operations on the Ureter, Dr. E. Granville Crabtree, Boston:** (a) For the Relief of Megaloureter Due to Congenital Deformity of the Lower Ureter.—Four cases. The ureter was cut longitudinally and a definite strip removed, decreasing the caliber. Care should be taken not to lift the ureter from its bed, as the attachments to the bed aid in the blood supply. Satisfactory results were obtained in two cases.

(b) For the Relief of the Short Congenital Ureteral Stricture at the Uretropelvic Junction.—Correction of a tight exit of the kidney pelvis was made by opening the pelvis, drawing the tightened area upward within the pelvis, and slitting it but not severing it longitudinally, allowing the excess ureter to remain within the pelvis. Two cases with good results shown.

**Recent Experiences With Ureteroenterostomy, Dr. George Gilbert Smith, Boston:** Two types of operation given: One, Coffey No. 2; and second, a group

of cases where the ureter was transplanted after the Wetzel method of a gastrotomy. The latter method would seem superior to the former. Twenty-four cases reported. Sixteen such were carcinoma of the bladder. Not a very great risk with the Wetzel method in selected cases.

**Obliteration of the Ureter in a Congenital Kidney With Hydronephrosis, Dr. David W. MacKenzie and Dr. Magnus I. Seng., Montreal (by invitation):** Interesting report of a nephrectomy case in which a second ureter from the pelvis ended blindly downward and a ureter from the bladder ended blindly upward, there being a segment missing. The remainder of the kidney was hydronephrotic.

**The Value of Hexamethylenamin and Mercurochrome Intravenously in Urology, Dr. George R. Livermore, Memphis, Tenn.:** The continued use of these drugs is shown to be applicable to a certain group of cases. Small doses should be given frequently.

**Tumors of the Spermatic Cord, Dr. William C. Quinby, Boston:** Few tumors and hydroceles reported. **Retroperitoneal Papilliferous Cyst-Adenocarcinoma, Report of a Case, Dr. Thomas P. Shupe, Cleveland:** Report of a single case. **Melanoblastoma of the Penile Urethra, Dr. Charles M. McKenna, Chicago:** Single case report.



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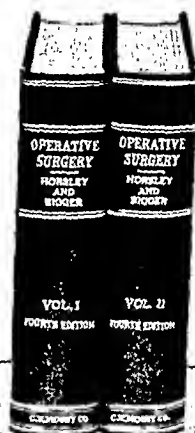
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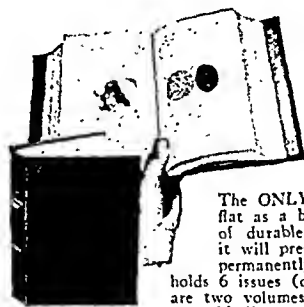
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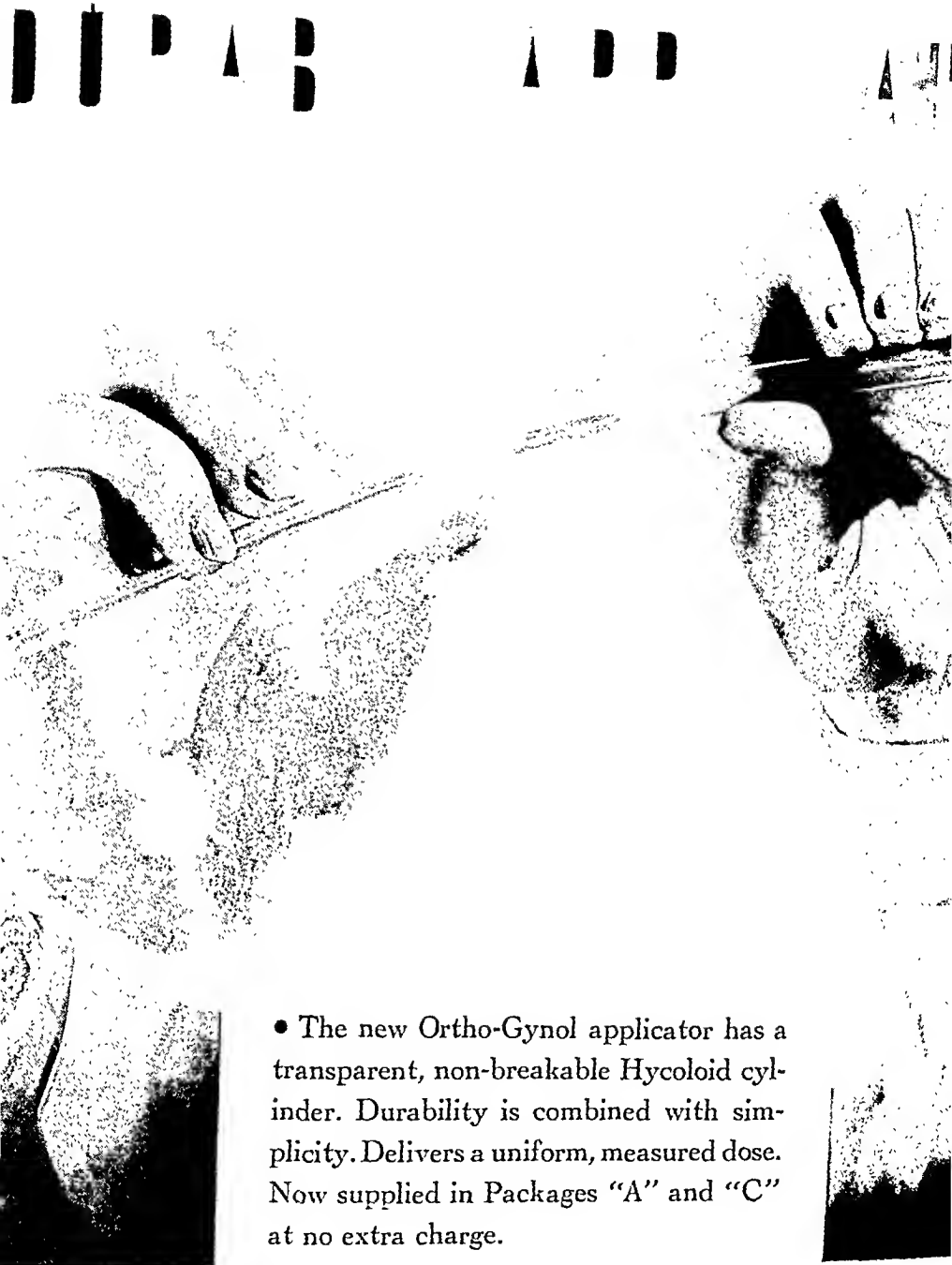
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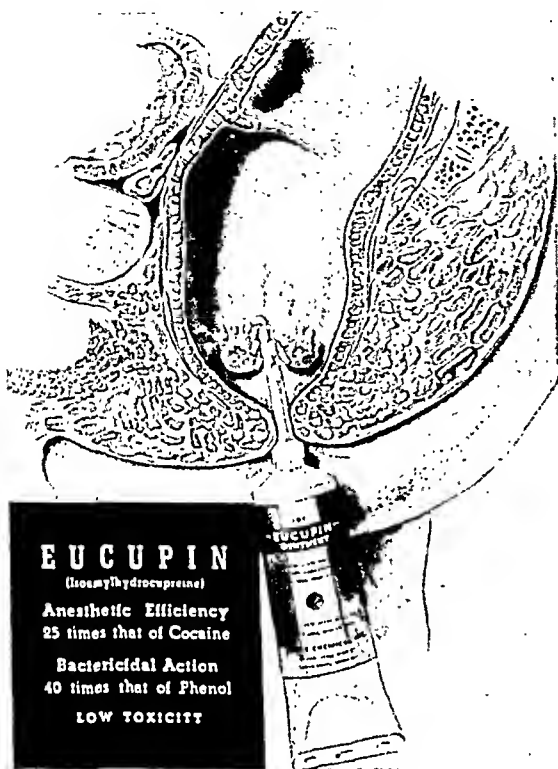
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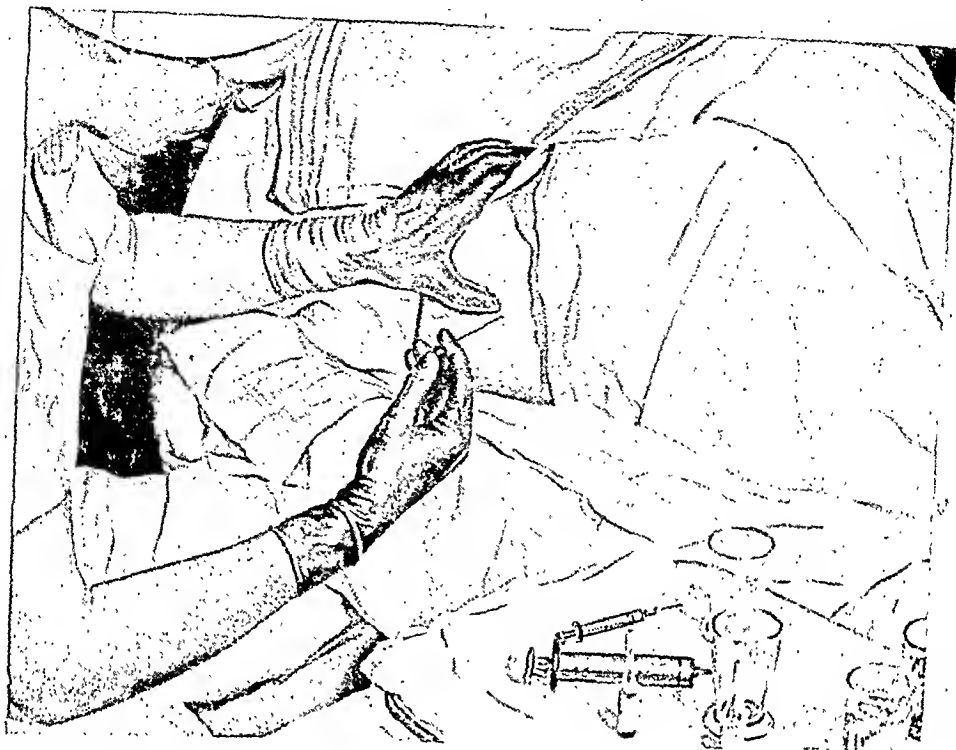
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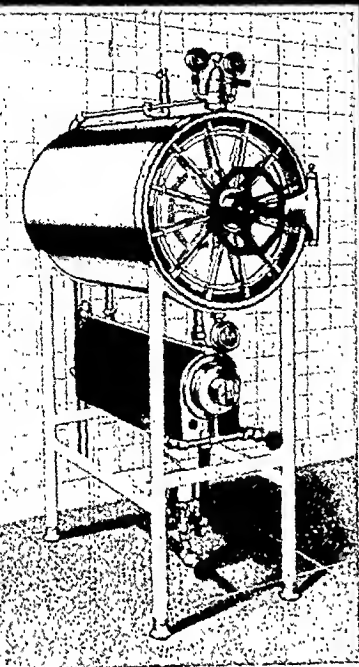
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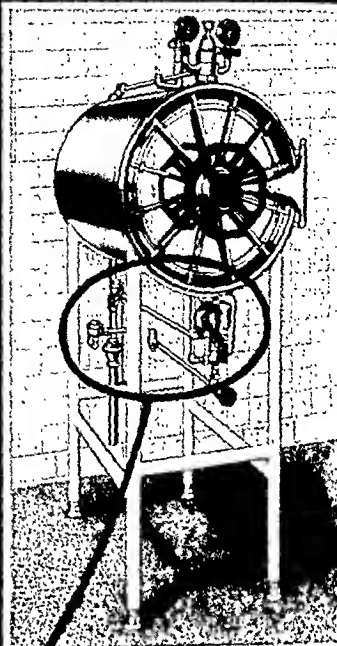
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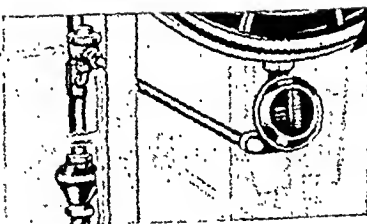
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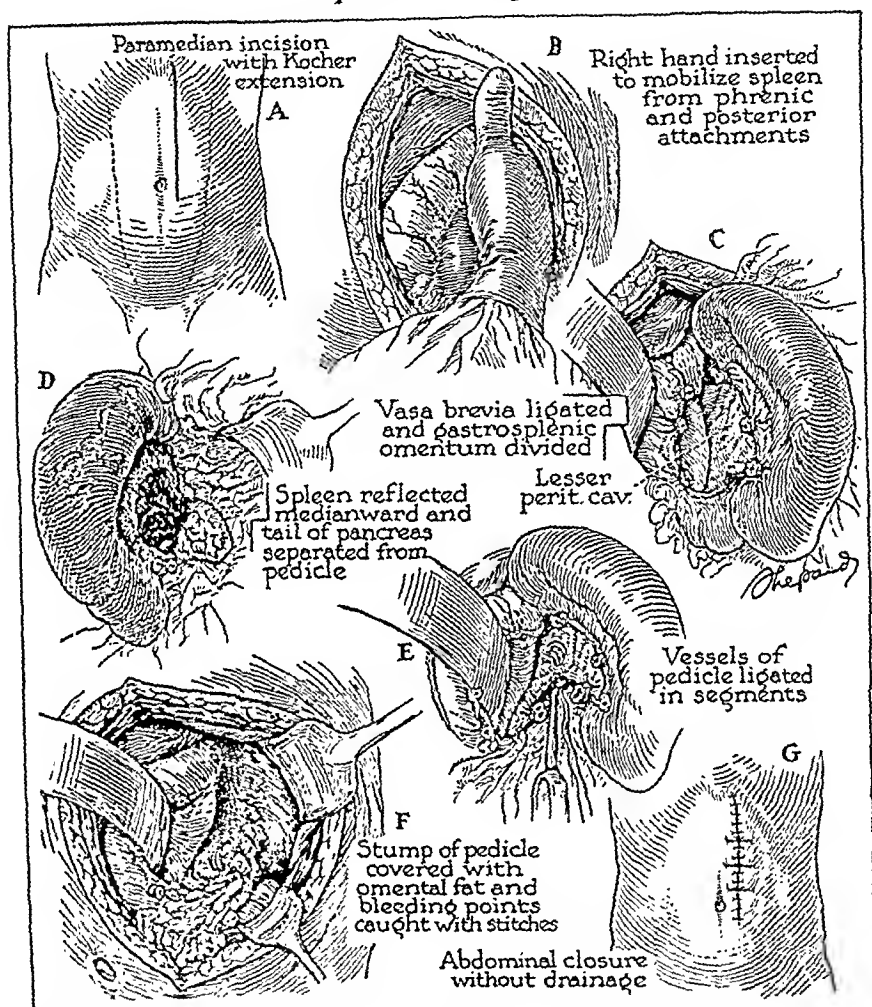
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# SURGERY

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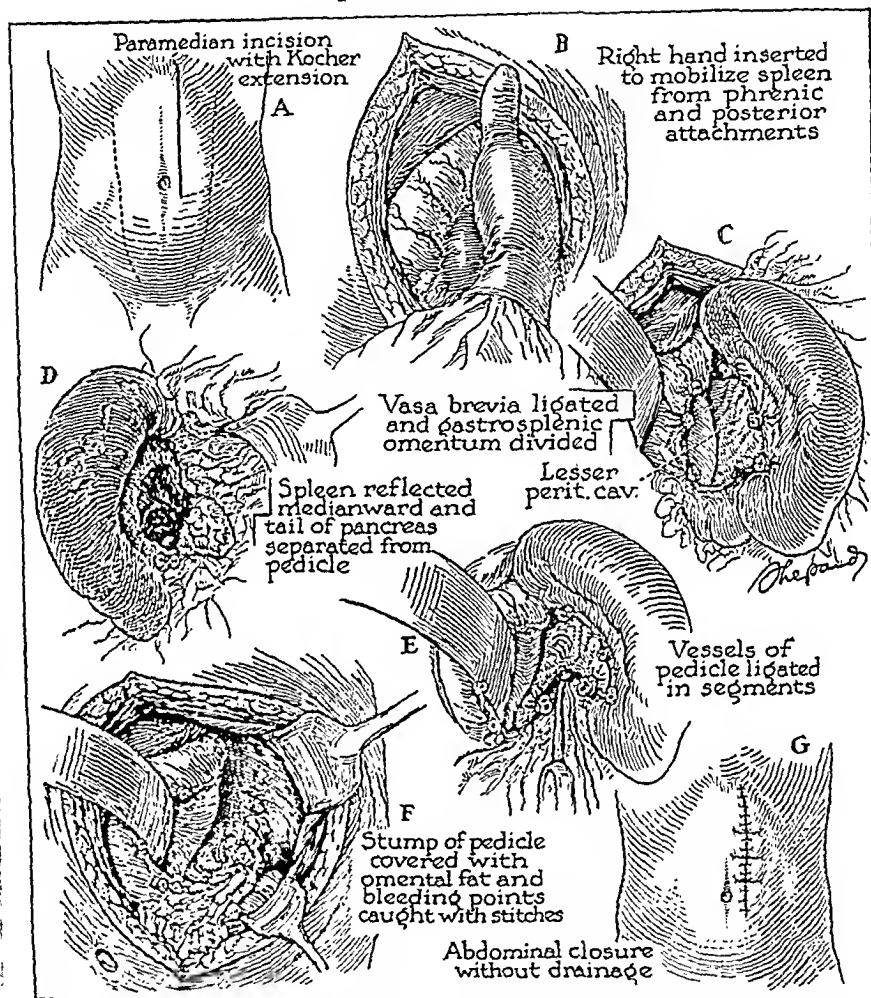
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# NOT AN ARMCHAIR SURGERY

During the World War there was always to be found a type of soldier who fought from the comfort of an armchair. Such soldiers were willing enough to tell how the fighting should be done, but they never did any of the actual fighting themselves. There are books on surgery written by armchair surgeons, men who are not at the operating room fronts. It is obvious that something must be lacking in this type of surgical literature. The set of surgical books described on this page is not armchair surgery. Every one of the men connected with this surgery can be found any day in the week in gown and mask, and with their surgical instruments in their clinics—and they write from the battle fronts where saving life is their chief concern. Take this into account when picking a text to add to your surgical library.

## OPERATIVE SURGERY

By J. SHELTON HORSLEY, M.D., LL.D., F.A.C.S., Attending Surgeon, St. Elizabeth's Hospital, Richmond, Va., and ISAAC A. BIGGER, M.D., Professor of Surgery, Medical College of Virginia, Surgeon-in-Chief, Memorial Hospital, Richmond, Va., with Contributions by G. C. COLEMAN, JOHN S. HORSLEY, JR., AUSTIN I. DODSON, and DONALD M. FAULKNER, In Two Volumes. 1357 pages, 1259 illustrations. Price, \$15.00.

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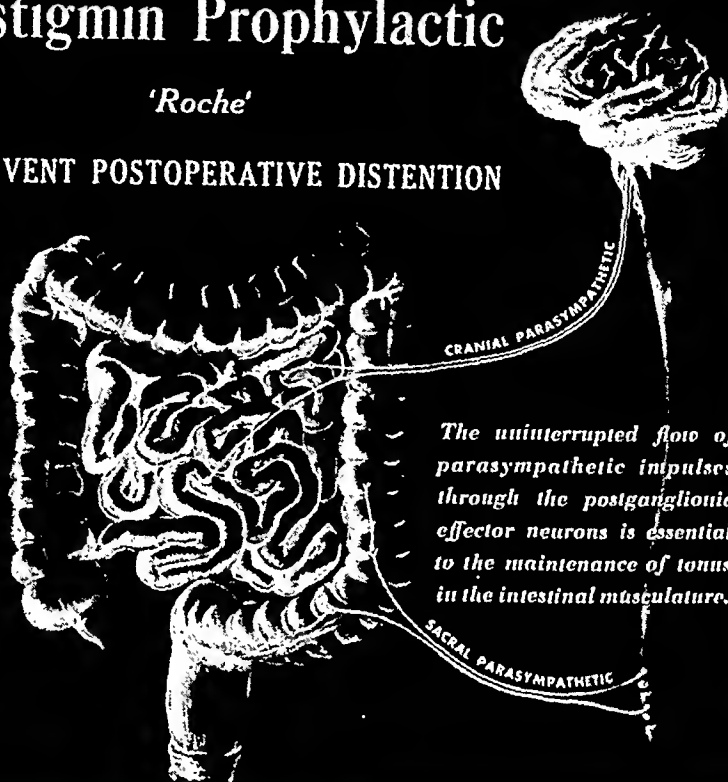
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# SURGERY

VOL. 2

AUGUST, 1937

No. 2

## Original Communications

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D. W. G. MURRAY, M.D., L. B. JAKES, M.A., T. S. PERRETT, M.D., AND  
C. H. BEST, M.D., TORONTO, CANADA

*(From the Department of Surgery, Department of Physiology, and the School of Hygiene, University of Toronto)*

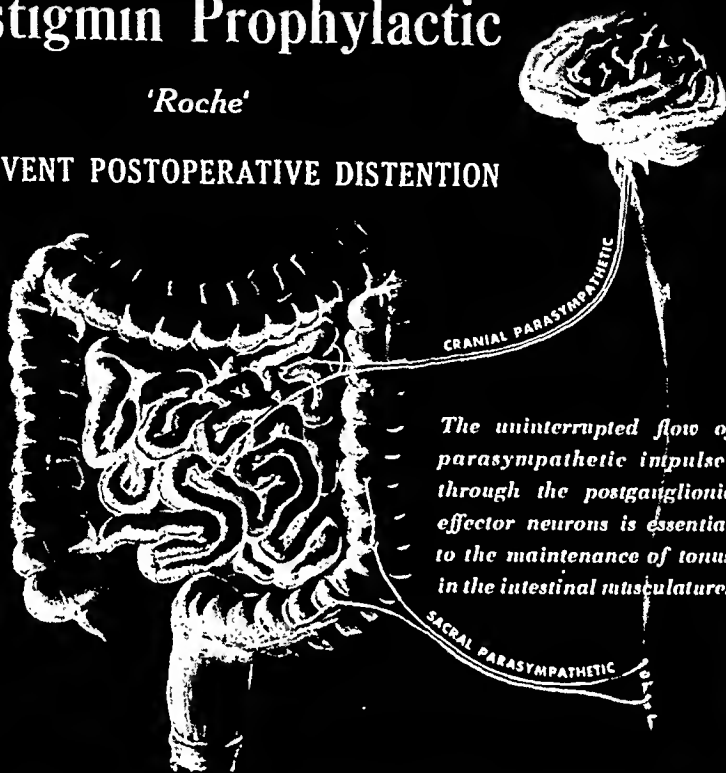
WHILE it is well established that heparin increases the coagulation time of blood, little or no experimental work on the effect of this anticoagulant on the thrombosis of blood vessels resulting from injury to the intima has been carried out. It has been shown by Zalm,<sup>1</sup> Eberth and Schimmelbunseh,<sup>2</sup> Weleh,<sup>3</sup> and Zurhelle<sup>4</sup> that thrombosis of blood vessels may be produced by the application of caustics or by mechanical injury to the intima. These procedures result in the accumulation of blood platelets on the wall of the vessel at the point of injury. Leucocytes then collect at the margin of and between the platelet masses. Fibrin is subsequently laid down. Since the methods of producing the vascular obstruction used in the experiments to be reported here are essentially similar to those employed by these previous investigators, the mechanism by which obstruction is brought about is presumably the same. We have examined the blood vessels at short intervals after injury in only a few cases and cannot, therefore, describe in detail the sequence of events leading up to the formation of a plug which caused, in most of the control experiments, cessation of blood flow in the injured veins. Since in this investigation lesions in peripheral veins in which the blood flow is sluggish were being studied, it was to be expected that the obstructing mass would be composed, in large part, of red cells and fibrin. We are informed, however, by Professor Robinson, of the Department of Pathology, and by our colleague in the School of Hygiene, Dr. D. L. MacLean, that the plugs are typical thrombi. In

Received for publication, March 8, 1937.

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The differences in coagulation time are no doubt due to the release of clotting factors from the traumatized areas. These difficulties can be eliminated, to a certain extent, by drawing the blood with a very small needle if certain precautions are used. The point of the needle is directed against the flow and is inserted some distance into the blood vessel. Each subsequent sample is secured from a slightly more peripheral point on the vessel. Care must be taken that the blood flows easily into the syringe and that no air enters during the withdrawal of the plunger. Even when attention is paid to these details, variations in the clotting time occur. If they are neglected, little significance can be attached to the end-point which is secured. The subsequent handling of the blood samples presents less difficulty. After testing most of the methods which have been advocated, we decided to use a mechanical device which eliminates subjective factors. The principle of our coagulometer is similar to that developed by Cannon and Mendenhall<sup>5</sup> and modified by Stoker.<sup>6</sup>

*Coagulometer.*—Two metal levers, *A* and *B*, are mounted on pinpoint bearings at *X* and *X*<sub>1</sub>. *A* is parallel to, and about 2 cm. above, *B*. At one end of each lever, weights *C* and *C*<sub>1</sub> are attached. These may be finely adjusted and locked at any point. At the opposite end of *A* is a fork which supports, between its arms, the plunger *D* (weight, 1.340 gm.). This plunger is constructed from monel metal and in shape resembles two shallow cones placed base to base. The diameter at the largest point is 8 mm. Into a hole bored through the apices is soldered a short length of monel wire. To the other end of the wire a cross-piece, to serve as a means of support when the plunger is suspended from the fork, is attached.

Between the fork and the fulcrum is attached a platinum point *E* which makes contact with a similar point *F* on the lever *B*. *F* is insulated from the lever *B*. These points are connected in series with the signal magnet *G*.

Under *B* is mounted an electromagnet *H* which, when charged, pulls down the lever *B* by means of the soft iron armature attached at *I*. When the circuit is broken, the lever will return to the horizontal because of the extra weight of *C*<sub>1</sub>. An adjusting screw at *J* controls the extent of this movement. As the weight of *A* is greater at the forked end, the points *E* and *F* will be held in close contact and the movements of *B* transmitted to *A* through these points.

The weight *C*, on *A*, is adjusted so that the lever will just remain horizontal when *D* is replaced by a standard weight of 1.000 gm.

In operation, 1 c.c. of blood is placed in the test tube *K* (10 mm. bore by 50 mm. high) and the height of the test tube adjusted so that the plunger is just clear of the bottom when the levers are held down against *H*. At intervals of one minute and for a period of three seconds the magnet *H* is stimulated. This pulls down the lever *B* and permits the plunger *D* to sink, by its own weight, in the blood. If the blood is not coagulated, contact is made at the points *E* and *F* and the signal magnet *G* will record this on a kymograph. If the blood is coagulated, the plunger will be supported by the clot and no contact will be made. A record in one-minute intervals is recorded on the kymograph. This record ceases when the blood is clotted.

An ordinary household electric clock is used to control the make-and-break mechanism for the electromagnets. The second hand is replaced by a tapered arm *M* which once in every revolution closes the contacts *N* and *O*. The wide end of the

some sections, accumulations of platelets are clearly visible, while in others the manner in which the formed elements are laid down distinguishes the obstructing mass from a clot.

In this study, injury to the lining of the veins was produced by two procedures. The first was mechanical and the second chemical. When a solution of purified heparin was administered intravenously for an adequate period, the incidence of obstruction by thrombus was very definitely less than in the experiments in which the anticoagulant was not used.

#### METHODS

Normal healthy dogs, weighing from ten to fifteen kilograms, have been used as experimental animals. Ether or nembutal has been

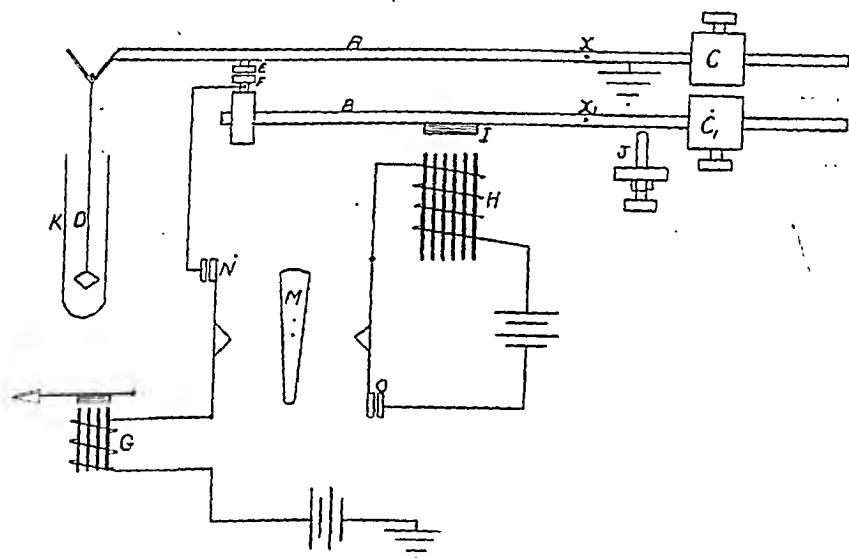


Fig. 1.

employed when anesthesia was necessary. In the determination of the coagulation time of the blood such great variation was found that considerable effort was made to secure a method which would give a consistent end-point. The difficulties of securing uniform results may be divided into two groups; first, those associated with the removal of the blood from the veins, and second, those involved in the subsequent care and handling of the sample. In confirmation of the results of previous investigators, it was found impossible to take repeated samples of blood, using a syringe and needle, from the same part of the vein without shortening the coagulation time very appreciably. The third and fourth samples would often gel before they could be placed in the recording apparatus. The same difficulty was encountered in obtaining samples from cannulas or from a sectioned artery.

finger. It is obvious that great care must be taken to use the same length of vein in all the experiments of one series. Unhappily, the calibers of the veins cannot readily be measured and must be assumed to be equal. If the volumes of blood in the occluded veins are not similar, the concentrations of soriein to which the intimal surfaces are exposed will vary. If branches of the veins can be detected, these are also occluded by pressure. The sodium ricinoleate solution is then injected and prevented from escaping from the vein by pressure over the point at which the needle entered. The solution is kept in this manner in the vein for a period of three minutes. The vein is then released.

*Method of Administering Heparin.*—In the preliminary stages of this investigation heparin was administered in a variety of ways. Certain descriptive terms have come into use in these laboratories. Local heparinization is the term used to describe the application of heparin to one particular area. This procedure was used in experiments on blood vessel surgery. Heparin was incorporated in vaseline or jelly and applied to the edges of the blood vessels about to be sutured. No significant result has been obtained by this method of administering the antieoagulant. Regional heparinization is the term used to describe the administration of heparin in such a way that the coagulation time of the blood of one limb, for example, is increased without materially affecting the blood in other parts of the body. Thus, with an infusion of heparin into the femoral artery of one limb, blood samples from the veins of the same leg show a longer clotting time than those secured at the same time from other parts of the body. This is true, however, only when small doses of heparin are administered. With larger doses more of the antieoagulant reaches the general circulation and the increase in clotting time is general. The term general heparinization describes the results of the administration of heparin into a vein or artery at such a rate that the clotting time of the blood from all parts of the body is increased. Most of the results which we are reporting in this paper were secured by general heparinization of experimental animals. The heparin was given intravenously by one of three methods. In preliminary experiments, a single injection was made by syringe. In a second series, a continuous injection of heparin dissolved in saline was made by means of a motor-driven pump. Animals receiving the antieoagulant by this procedure were maintained under nembutal anesthesia and the injection was continued for, at most, ten hours. The third method was by a continuous injection of heparin in saline, utilizing, with slight modifications, the technique adopted by Jacobs,<sup>7</sup> of Chicago. By this procedure it is possible to give continuous intravenous infusions to dogs for long periods of time without seriously interfering with their activity. Ether anesthesia was used during the insertion of a cannula



lever *M* holds the points *O* in contact for three seconds while the narrow end closes the points *N* for one second. Contact at *N* should synchronize with the third second of contact at *O*. If contact is made earlier or later, a misleading record may be made. The contact points *N* and *O* should be mounted on the clock face, one a little in front of the other, and the lever *M* attached slightly off the right angle. If mounted in the same plane, contacts would be made at thirty-second intervals.

The apparatus in use is composed of four of the above units. One electric clock is sufficient to operate all four. The levers *B* are secured firmly to a shaft carried by two end-bearings. This shaft has attached to it an extra lever, carrying a weight at one end and an armature, similar to that shown on *B*, at the other. The weight is sufficiently heavy to balance all the levers. By this means the four units are operated by one magnet.

In an endeavor to obtain accurate checks on the blood contained in the four tubes and filled from the same sample, the test tubes are partially immersed in a constant temperature water-bath which is kept at 37° C. The tubes are held in place by spring clamps attached to one side of the bath.

The weights of the plungers are adjusted to within 2 mg., and as the levers are balanced to the standard weight of 1.000 gm., the downward pressure exerted by any plunger is equivalent to 0.340 gm. (weight of *D* [1.340 gm.] - 1.000 gm.).

*Method of Producing the Injury to Veins.*—A. Mechanical means: The blood vessels chosen for these experiments were the readily accessible radial and saphenous veins. Very little dissection was needed to free them from the surrounding tissue. The skin incision was made at some little distance to the side of the vein and the skin undercut so that, when sewing up, the flap would fall over the vein. After about one inch of the vessel had been isolated in this way, a needle carrying a length of silk thread (size 000) was passed up through the lumen of the veins for about three-quarters of an inch so that the thread remained within the vessel wall. The vein was then crushed against the thread between the jaws of a pair of artery forceps. The forceps were elamped very tightly on the vein. The crushing was continued along the full length of the exposed vein and then repeated in at least two other planes. In later experiments, a pair of forceps with a particularly firm grip was selected and used only for the purpose of crushing. After the injury the thread was withdrawn, bleeding controlled with gauze, and the wound closed by interrupted silk sutures. The veins were left in situ for periods ranging from seven hours to seven days. They were then removed between ligatures, examined in the gross, and placed in formalin as the first stage in their preparation for microscopic examination.

B. Injury produced by injection of sodium ricinoleate (soricin): The second method of producing occlusion of the veins was by the injection of a solution of sodium ricinoleate. This was a commercial preparation manufactured by the Wm. S. Merrell Company, Cincinnati, U. S. A. The needle of the syringe containing the soricin is introduced through the skin into the vein. The vein is then occluded one or one and one-half inches above the needle by pressure with the

tients when he injected 1 mg. of heparin per 10 c.c. of blood. This preparation contained 10 units per milligram. In our experience, the 5 unit material, which was the only preparation readily available when these experiments were started, exerted marked toxic effects when administered intravenously to dogs. Some of these dogs died and at autopsy revealed marked hemorrhages in the intestine. Later, using more highly purified heparin, 75 units per milligram, no deaths were produced in a series of some twenty dogs studied. Vomiting and pronounced muscular weakness were, however, not infrequently observed when large doses of the material were used. Recently we have employed more highly purified heparin and in some sixty dogs which received a preparation with a potency of about 250 units per milligram, for a period of seventy-two hours (500 mg.; i.e., 125,000 units of heparin in all were injected), no signs of a toxic action of the anticoagulant were detected.\*

Tests for the toxicity of this heparin containing 250 units per milligram were made upon various species of animals. Rabbits, guinea pigs, and mice were injected with sufficient of the material to render their blood incoagulable for very long periods of time. No toxic effects were produced. These findings have, however, relatively little significance in view of the fact that heparin has been much further purified by our colleagues Charles and Scott since the studies of toxicity referred to above were carried out. More recently we have had available adequate amounts of heparin of a potency of 500 units per milligram. This is dissolved in distilled water or saline and 1 c.c. of this solution usually contains approximately 15,000 units of the anticoagulant. The effect on human subjects will be described in more detail later, but it may be stated here that the 250-unit heparin produced definite signs of toxicity. More highly purified material, however, has been given to patients with no deleterious effects. Since adequate amounts of this relatively innocuous and very potent material are now available, it is unnecessary to describe in detail the results of toxicity tests on the cruder preparations.

#### EXPERIMENTAL RESULTS AND COMMENTS

*Injury Produced by Mechanical Means.*—When the veins of a dog are crushed upon a thread inserted in the lumen, as described under Methods, thrombosis will take place in only a limited number of the veins unless considerable force is applied in the crushing process. If force is exerted and extensive damage to the veins produced, a thrombus will form, according to our experience, in approximately 80 per cent of the cases (Table I). If this thrombus is left in situ for five or six days it is usually found, upon removal of the veins, that it entirely fills the lumen and is adherent to the vein wall. The

\*We are indebted to Miss Winifred Chute for help in some of the early experiments.

into the external jugular vein. The cannula was connected by a flexible metal tube to a reservoir containing the heparin solution. After recovery from the anesthetic, the animal moved about with considerable freedom. The rate of injection was maintained at a constant level by a motor-driven pump. The injections by this method were usually continued for seventy-two hours. The parts of the apparatus which it was not feasible to sterilize by heat were thoroughly bathed with antiseptic solution before each experiment.

#### THE TOXICITY OF HEPARIN

Since it was our hope that heparin might ultimately be safely used in human patients, the toxicity of the various preparations of this anticoagulant was a very important matter. It is evident from the literature and from our own findings that the toxicity varies greatly and, in general, inversely as the purity of the preparation.

The Howell unit of heparin is the amount which will prevent the clotting of 1 c.c. of cat's blood for twenty-four hours. Even when precautions are taken with regard to temperature, stirring, etc., it is impossible to estimate the potency of the solution accurately by this procedure without the use of a standard preparation. However, if a standard heparin is used and the unknown preparation compared with this, reliable results may be obtained. A standard of heparin has been set up in the Connaught Laboratories and the heparin which we have used has always been compared with this preparation.

Using heparin of a potency of 15 units per milligram, Howell and McDonald<sup>8</sup> injected an amount into a dog which was sufficient to render its blood incoagulable. This was approximately 0.45 mg. per kilogram. This injection was repeated daily for five days. They reported no demonstrable change in the red and white blood counts or in the platelets. There was no indication of any deleterious effect on the animal. Reed<sup>9</sup> injected moderate quantities of heparin intravenously in normal and etherized dogs and rabbits. He found no change in temperature, no cardiovascular effect, no concentration of the blood cells, and no abnormalities in respiration. In 1924, Mason<sup>10</sup> reported on the use of material containing 5 units per milligram. He added from 50 to 300 mg. to blood used in transfusing human patients. In about one-half the cases he observed reactions which varied from slight chills to severe headache, high fever, and nausea. Mason concluded that while the heparin used in the early part of his work was too toxic to warrant its routine clinical use in doses of 100 mg. (500 units), preparations subsequently made had given encouraging results. Howell<sup>11</sup> reported upon the use of heparin containing 100 units per milligram in transfusions given to human subjects. He reported a slight reaction in two of the ten transfusions carried out on six patients. Godlowski<sup>12</sup> found no evidence of toxicity in his pa-

tients when he injected 1 mg. of heparin per 10 c.c. of blood. This preparation contained 10 units per milligram. In our experience, the 5 unit material, which was the only preparation readily available when these experiments were started, exerted marked toxic effects when administered intravenously to dogs. Some of these dogs died and at autopsy revealed marked hemorrhages in the intestine. Later, using more highly purified heparin, 75 units per milligram, no deaths were produced in a series of some twenty dogs studied. Vomiting and pronounced muscular weakness were, however, not infrequently observed when large doses of the material were used. Recently we have employed more highly purified heparin and in some sixty dogs which received a preparation with a potency of about 250 units per milligram, for a period of seventy-two hours (500 mg.; i.e., 125,000 units of heparin in all were injected), no signs of a toxic action of the anticoagulant were detected.\*

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incidence of obstruction by thrombus formation in a vein which has been injured, as described above, is extremely small as long as the animal is maintained under the influence of heparin. An experiment of this nature was conducted in which thirteen veins were observed. Following a single injection of heparin the veins were damaged, but they were removed before the effect of the heparin had worn off. All the veins of this group except three were perfectly clear on macroscopic examination. In these three, a small thrombus was present on a portion of the wall. Without heparin the veins (i.e., 80 per cent of them) are found to be obstructed by thrombus when examined forty minutes after injury.

TABLE I

METHOD OF INJURY	NO. OF VEINS	PATENT	OCCLUDED	PARTIALLY OCCLUDED	PER CENT OCCLUDED
Crushing—moderate, no thread used	10	9	1	0	10
Crushing—moderate, thread used	10	6	4	0	40
Crushing—severe, thread used	57	8	44	5	80

It was found that an adequate effect was produced upon the coagulation time of blood in dogs; i.e., the coagulation time was maintained at approximately thirty minutes, when relatively crude heparin was administered intravenously at the rate of 3.3 units per kilogram per minute. In the next experiment to be described, heparin was given intravenously in saline solution at this rate. The veins were traumatized and the injection continued for seventy hours. At the end of this time the veins were excised and examined. Four veins of one dog were used in this experiment. They were all perfectly clear and no trace of thrombus could be found. Further details of these experiments and of the results obtained are given in Table II.

TABLE II

NO. OF VEINS	HEPARIN MG./KG.	CALCULATED HEPARIN EFFECT	VEINS LEFT IN SITU	PATENT	OCCLUDED	PARTIALLY OCCLUDED
13	5 60*	1½ hr.	1 hr.	5	0	
	6 140*	3½ hr.	3 hr.	6	0	2 (very small thrombus)
	2 180*	4½ hr.	4 hr.	2	0	1 (very small thrombus)
4	0.22 mg./kg./min.	70 hr.	70 hr.	4	0	

\*Single injection.

In the next series of experiments, thirteen veins were studied in animals which had received a single injection of heparin. The vein was traumatized immediately after the injection of heparin had been made but was left in situ for periods of from three and one-half to

twenty-four hours. The amount of heparin injected varied in the different experiments. The results of this series are given in Table III. It will be noted that of the thirteen veins one was partly occluded while the remaining twelve were completely filled with thrombus and clot.

TABLE III

NO. OF VEINS	HEPARIN MG./KG.	CALCULATED HEPARIN EFFECT	VEINS LEFT IN SITU	PATENT	OCCCLUDED	PARTIALLY OCCCLUDED
1	60	1½ hr.	3½ hr.	0	0	1
8	100	2½ hr.	4½ hr.	0	8	0
4	180	4½ hr.	24 hr.	0	4	0

In the next series of experiments single injections of heparin (approximately 6,000 units) were given to 10-kilogram dogs. The veins were then damaged and an infusion of heparin in saline solution started immediately. This was maintained at a rate of 2.2 units per kilogram per minute for from seventy to seventy-two hours. The veins were inspected seven days after they had been injured. Nine veins were treated in this manner. Six of these showed clear lumina and a smooth, glistening intima. Three were occluded by thrombi. In one of these the obstruction was at the site of a valve to which the thrombus was attached. In the other two cases the veins were exposed for some time on the surface of an infected wound (Table IV).

TABLE IV

NO. OF VEINS	HEPARIN GIVEN	EXAMINED	PATENT	OCCCLUDED	PARTIALLY OCCCLUDED
9	72 hr.	7 days after injury	6	3*	0

\*One thrombus attached to valve curtain: 2 veins exposed on surface of infected wound.

In the next group of experiments a vein on one side of an animal was traumatized, but no heparin was administered. This vein was examined seven to twenty-four hours later and if obstructed the corresponding vein on the other side of the animal was similarly traumatized after the injection of heparin had been started. In this group of experiments with ten control veins and ten under test, one of the controls was only partially occluded while one of the veins which had been bathed with heparin became completely plugged by thrombus. There is, perhaps, an explanation for this latter case in that the pump which was forcing the heparin into the animal stopped and the full dose of the anticoagulant was not received (Table V).

In the next series 28 veins were studied. The procedure was the same as in the preceding experiment, with one exception. The control veins, i.e., those which were not bathed by heparin, instead of being examined in 7 to 24 hours, were left in situ for 7 days. Heparin

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In the next series 28 veins were studied. The procedure was the same as in the preceding experiment, with one exception. The control veins, i.e., those which were not bathed by heparin, instead of being examined in 7 to 24 hours, were left in situ for 7 days. Heparin



TABLE V

RIGHT VEINS (CONTROLS)—EXAMINED AND EXCISED IN 7 TO 24 HOURS  
 LEFT VEINS (HEPARIN)—HEPARIN 72 HOURS—EXAMINED 7 DAYS AFTER INJURY

RIGHT VEINS (NO HEPARIN)					LEFT VEINS (HEPARIN GIVEN)					
NO. OF VEINS	EXAMINED	PATENT	OCCCLUDED	PARTIALLY OCCCLUDED	NO. OF VEINS	HEPARIN GIVEN	EXAMINED	PATENT	OCCCLUDED	PARTIALLY OCCCLUDED
10	7-24 hr.	0	9	1	10	70 hr.	7 days	9	1*	0

\*The pump stopped overnight and the full amount of heparin was not received.

was administered for a period of 70 hours and the test veins were left in place for 6 days after the traumatization. The results of these series are shown in Table VI.

TABLE VI

RIGHT VEINS (CONTROLS)					LEFT VEINS (HEPARIN GIVEN)					
NO. OF VEINS	EXAMINED	PATENT	OCCCLUDED	PARTIALLY OCCCLUDED	NO. OF VEINS	HEPARIN GIVEN	EXAMINED	PATENT	OCCCLUDED	PARTIALLY OCCCLUDED
14	7 days	4	8	2	14	70 hr.	6 days	11	3*	0

\*In 2 of these cases there was an extensive hematoma.

While it is very difficult to summarize the results of these experiments in which injury to the veins had been produced by mechanical means, this is attempted in Table VII. When no heparin was given,

TABLE VII

NO HEPARIN					HEPARIN					
NO. OF VEINS	EXAMINED	PATENT	OCCCLUDED	PARTIALLY OCCCLUDED	NO. OF VEINS	HEPARIN GIVEN	EXAMINED	PATENT	OCCCLUDED	PARTIALLY OCCCLUDED
10	7-24 hr.	0	9	1	4	70 hr.	70 hr.	4	0	0
14	7 days	4	8	2	9	70 hr.	7 days	6	3	0
33	7 hr.-7 days*	4	27	2	10	70 hr.	7 days	9	1	0
					14	70 hr.	7 days	11	3	0
Totals 57		8	44	5	37			30	7	0

\*Four of these veins were removed and examined after 7 hr.; 9 after 24 hr.; 8 after 48 hr.; 4 after 5 days; and 8 after 7 days.

8 of the 57 veins examined were, macroscopically, free of thrombus. (The 33 veins of the control series in this table were referred to in Table I. They were included in the group consisting of 57 veins.)

Of 37 cases in which heparin was administered to the animals, 30 of the 37 veins were free of thrombus as judged by macroscopic examination. The figures are taken from all the experiments in which heparin was administered for prolonged periods.

*Injury Produced by Chemical Means.*—The procedure used in damaging the intima of the veins by chemical means has been described under Methods. After some preliminary experiments had been carried out, we studied the effects of heparin on injury produced when 0.25 c.c. of soricin was injected into each vein. Some 204 veins were studied in this series. No useful purpose will be served by describing the experiments in great detail. The results are summarized in Table VIII. It will be observed that of the 114 veins from animals which

TABLE VIII

NO. OF VEINS	CONTROLS			HEPARIN				
	OCCLUDED	PATENT	PER CENT OCCLUDED	OCCLUDED	PATENT	PER CENT OCCLUDED	HEPARIN U./KG./HR.	HEPARIN GIVEN
204	97	17	85	44	46	47	22.5	66-72 hours

0.25 c.c. soricin injected in all veins. Controls, 15 per cent patent; heparin, 53 per cent patent.

received no heparin, 85 per cent were occluded. Of the 90 veins investigated from animals which received heparin, 47 per cent were occluded. In other words, 15 per cent of the control veins were patent while 53 per cent of those which had received heparin were open after from 4 to 7 days. The obvious deduction from the results of this large series of experiments is that heparin in the dose used, i.e., 22.5 units per kilogram per hour, is not nearly so effective as might be desired in preventing thrombosis of veins. While a dose of 0.25 c.c. of soricin, under the conditions which we have described, does not produce occlusion in all cases, it was thought expedient to determine whether smaller doses might not be nearly as effective. An injection of 0.15 c.c. of soricin was tried in a series of 24 veins. The results in Table IX show that in 83 per cent of the control series the

TABLE IX

NO. OF VEINS	CONTROLS			HEPARIN				
	OCCLUDED	PATENT	PER CENT OCCLUDED	OCCLUDED	PATENT	PER CENT OCCLUDED	HEPARIN U./KG./HR.	HEPARIN GIVEN
14	10	2	83	0*	12	0	22.5	68-73 hours

\*A very small thrombus which produced no obstruction of blood flow was found in one vein.

0.15 c.c. soricin injected in all veins. Controls, 17 per cent patent; heparin, 100 per cent patent.

veins were occluded by thrombi. When heparin was given in the dose which was used in most of the previous experiments, 11 of the 12 veins were completely free of thrombus. In 1 vein, while there was no interference with blood flow through it, there was a small thrombus firmly attached to the wall. Interestingly enough, this thrombus was composed almost entirely of platelets. These results appear to show that if a small dose of soriein is used, its effect, so far as the obstruction of veins is concerned, may be almost completely counteracted by an adequate dose of heparin administered continuously for a period of approximately 70 hours.

It may be noted here that if the veins are examined before the injection of heparin is discontinued, thrombosis is not observed in most cases even when much larger doses of soriein are used (up to 1.0 c.e.). Under these circumstances, thrombosis would presumably have occurred invariably soon after the effect of heparin had worn off. These higher concentrations of soriein produce almost complete destruction of the tissue with which they come in contact. Our findings also suggest that the animals should always be thoroughly heparinized before the injury to the veins is produced, if the action of the anticoagulant in preventing obstruction is to be most effective.

*Regional Heparinization in Experimental Animals.*—A large number of experiments in which attempts have been made to heparinize one limb of an experimental animal without affecting the blood in other parts of the body have been carried out. It will be sufficient for our present purpose to describe one experiment in some detail.

A dog weighing approximately 7 kg. was anesthetized by an intravenous injection of nembutal. Both femoral arteries and veins were exposed. The clotting time of the blood from the vein of the right leg was 5 minutes, and of that from the left leg, 4 minutes. Heparin solution was then introduced from a buret through a needle into the right femoral artery. The solution contained approximately 2,200 units per cubic centimeter. Ten minutes after the injection had been started, the clotting time of the blood secured from the vein of the heparinized limb was 11 minutes, while that from the unheparinized extremity was 5 minutes. Thirty-five minutes after the start of injection, blood from the right femoral vein showed a clotting time of 11 minutes, while 15 minutes later blood secured from the unheparinized left limb showed a clotting time of 6 minutes. The heparin solution was injected at the rate of approximately 0.7 c.e. per minute. Four hours and thirty minutes after the start of the injection the clotting time on the heparinized side was 21 minutes, while on the other side the time was 20 minutes. The results of this experiment show that regional heparinization can be accomplished, for a time at least, when an injection of heparin solution is made intraarterially at a fairly slow rate. After some time, however, in many of the experi-

ments the clotting time of blood from other parts of the body showed the effects of heparin; i.e., the heparinization had become general. It is possible, of course, that if the rate of injection had been decreased regional heparinization might have been maintained.

*Observations on Human Subjects.*—While a more detailed report will be made later on the results of the use of heparin in human subjects, a summary of the findings we have secured will be included here. The objective in these investigations was merely to determine the toxicity of the heparin preparations on human subjects and the effect on the clotting time of the blood.

The first administration of heparin to a patient on the surgical ward of the Toronto General Hospital was carried out on April 16, 1935. The brachial artery of the left arm was exposed by a small incision under local anesthesia. A needle was inserted in the artery and the heparin solution was injected by means of a motor-driven pump. To make this solution, heparin powder with a potency of approximately 250 units per milligram was dissolved in saline solution and the mixture sterilized by passage through a Berkefeld filter. Samples of blood from the veins of the injected arm showed a rise in clotting time from the normal of 6 minutes to a value approximately 18 minutes. Samples of blood from other parts of the body showed, at this time, no change in clotting time. This is an example of regional heparinization in a human subject. The injection was maintained for a period of approximately 4 hours and no signs of any toxic effects were observed. Regional heparinization was carried out in several other cases.

No evidence has been obtained in experimental animals or human subjects that a negative phase, i.e., a decrease in coagulation time, develops when the injection of heparin is discontinued.

The general heparinization of the human subject was attempted on several occasions with relatively crude heparin. Toxic effects in the form of weakness, headache, and slight chills made it inadvisable to continue the injections. More recently, using heparin of a potency of 250 units per milligram, 4 of 9 clinical cases showed no toxic effects even after prolonged injection. The other 5 of these cases, however, did exhibit definite signs of toxicity and the injections of heparin had to be discontinued. The effect of a single large dose of this preparation of the anticoagulant (22,000 units) rapidly administered to a patient is illustrated in Fig. 2. This patient was receiving heparin continuously at a slow rate and had been given an injection of 11,000 units one hour and ten minutes before the larger amount was administered. The rise in blood clotting time after the last injection may have been due, in part, to the effects of the previous dose.

More recently large amounts of highly purified heparin, 500 units per milligram, have been available. In the course of the purification

veins were occluded by thrombi. When heparin was given in the dose which was used in most of the previous experiments, 11 of the 12 veins were completely free of thrombns. In 1 vein, while there was no interference with blood flow through it, there was a small thrombus firmly attached to the wall. Interestingly enough, this thrombus was composed almost entirely of platelets. These results appear to show that if a small dose of soricin is used, its effect, so far as the obstruction of veins is concerned, may be almost completely counteracted by an adequate dose of heparin administered continuously for a period of approximately 70 hours.

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quently raised to a much higher level but, as stated above, no deleterious effects were observed. The cases which received heparin post-operatively had undergone one of the following operations: appendectomy, herniotomy—with and without living sutures—resection of colon, closure of colostomy, partial gastrectomy, drainage of empyema, bone graft of the tibia and of carpal scaphoid, or various minor operations such as excision of cysts, lipomata, and so on. In only one of these cases was there a hematoma at the site of operation. This was in the skin and while it may be attributed to heparin, it is also possible that it was due to inadequate hemostasis. The injections of heparin were commenced in from 2 to 3 hours after the completion of the operation.\*

*Histologic Findings.*—The histologic picture of veins thrombosed as a result of mechanical injury has been described by previous investigators. Our findings recorded in the tables are based on gross examination. Histologic sections were prepared of all the veins and the findings support, in general, those of the gross examination. In some cases platelet thrombi were found under the microscope in veins which had been considered on gross examination to be perfectly clear. Many of the heparinized veins, however, appeared to be completely free of thrombi, but in some of these inflammatory areas of varying sizes were present in the media or adventitia. These findings are based on examinations of several sections, but serial sections were not made.

The veins into which soricin had been injected and which subsequently became obstructed contained, on histologic examination, a mixed thrombus. If this examination was conducted twenty-four hours after the injection of the irritant, the veins were found to exhibit loss of endothelium from part of the wall and substitution of this by a line of fine dark-staining granular matter. This was probably a mixture of disintegrated nuclei and soricin. The media of these veins showed varying degrees of degeneration. In some cases a large area of this layer failed to take the nuclear stains. In other cases the nuclei and fibers stained well. The former were pyknotic and broken into fine granules. The muscle fibers were separated by widely dilated capillaries and in some cases by interstitial hemorrhage. The adventitia showed changes in some cases and not in others. If any of the irritant material which was injected had leaked out of the vein, there was a marked inflammatory reaction. The thrombus examined at this stage usually filled the entire lumen and was attached over a fairly large area of the vein wall by platelets and a network of fibrin in which red and white cells were visible.

\*A report of the earlier part of this work was presented before the Junior Inter-Urban Surgical Club of Canada in October, 1935.

of this substance, Charles and Scott were able to remove rather large quantities of a tarlike material which it is believed may have been responsible for the toxic properties of the cruder preparations. Seventy-six postoperative cases have now received injections of the

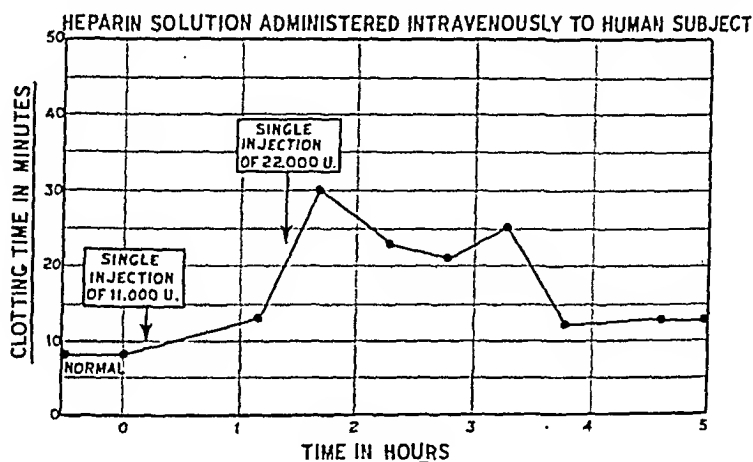


Fig. 2.

solutions of purified heparin by the intravenous route. The period of injection has usually varied from 24 to 120 hours. An effort has been made to keep the clotting time at approximately 15 to 20 minutes, i.e., at least two or three times the usual normal range, but very

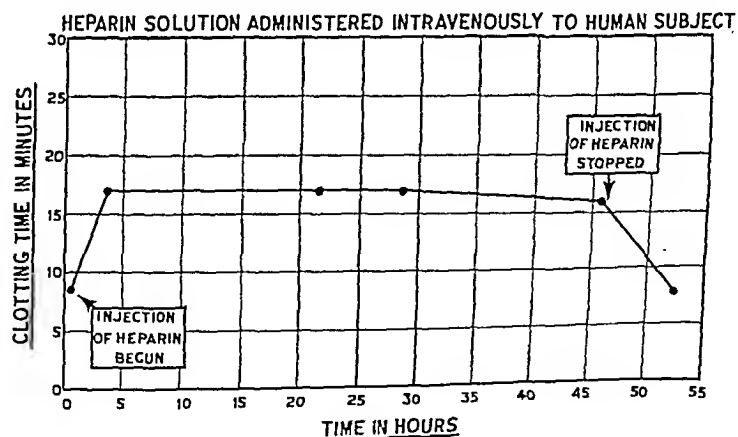


Fig. 3.

high values (51 minutes) have sometimes been observed. The results on one of these cases are illustrated in Fig. 3. The findings in this case are more regular than in some of the others and it has been chosen for this reason. In other cases the clotting time was fre-

quently raised to a much higher level but, as stated above, no deleterious effects were observed. The cases which received heparin post-operatively had undergone one of the following operations: appendectomy, herniotomy—with and without living sutures—resection of colon, closure of colostomy, partial gastrectomy, drainage of empyema, bone graft of the tibia and of carpal scaphoid, or various minor operations such as excision of cysts, lipomata, and so on. In only one of these cases was there a hematoma at the site of operation. This was in the skin and while it may be attributed to heparin, it is also possible that it was due to inadequate hemostasis. The injections of heparin were commenced in from 2 to 3 hours after the completion of the operation.\*

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The site of injection sometimes involved a valve area and in these cases the thrombus was often found attached to one of the valve leaflets.

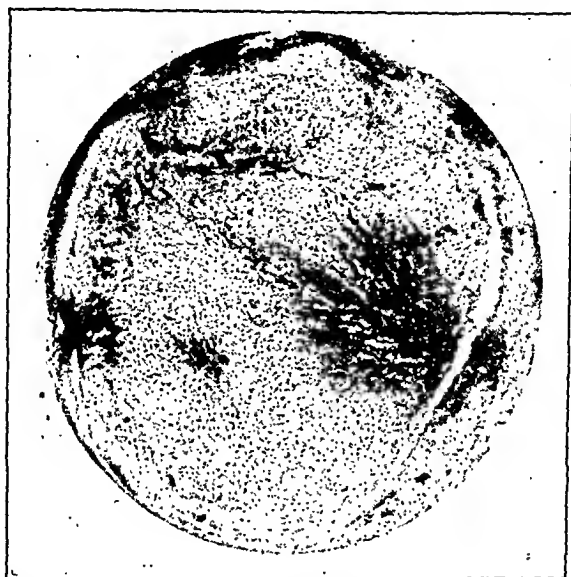


Fig. 4.—Photomicrograph of vein showing complete thrombosis. 0.25 c.c. soricin, excised after seventy-two hours. (H. and E. stain  $\times 75$ .)

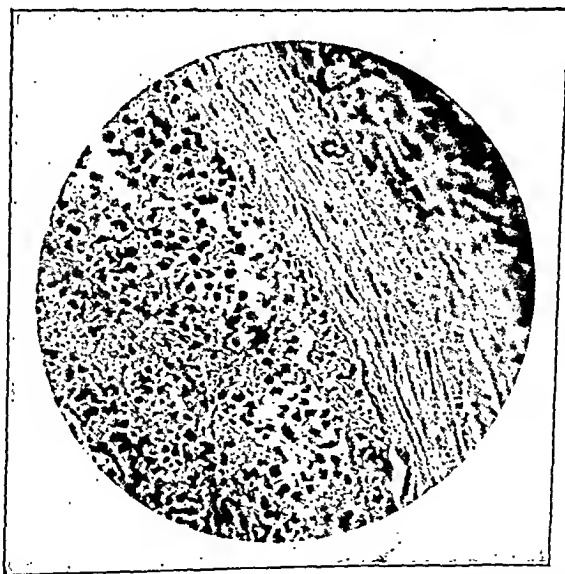


Fig. 5.—Section of same vein as shown in Fig. 4. (H. and E. stain  $\times 750$ .)

In 72 hours after the injection, the media usually took a nuclear stain. The nuclei, however, were broken and disintegrated and the

spaces between the muscle fibers were filled with phagocytic cells containing dark-staining granules and red cells. The thrombus filling

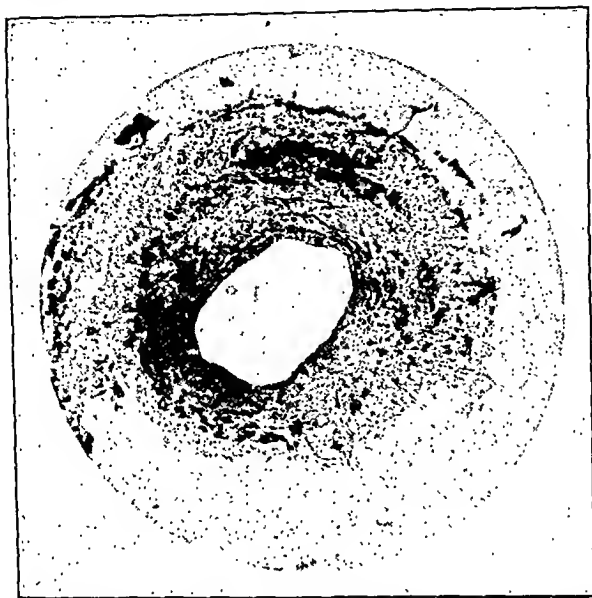


Fig. 6.—Photomicrograph of vein showing no thrombosis. 0.25 c.c. soricin, heparin sixty-five and a half hours, excised on seventh day. (H. and E. stain  $\times 75$ .)

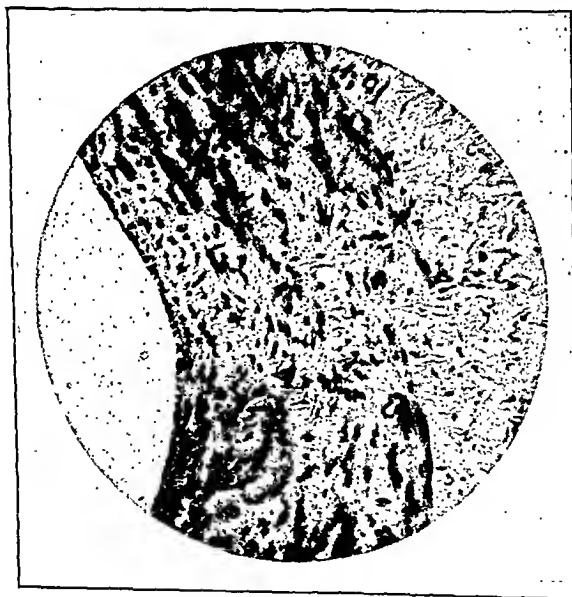


Fig. 7.—Section of same vein as shown in Fig. 6. (H. and E. stain  $\times 375$ .)

the lumen appeared to be attached directly to the media in some places from which heavy fibrin threads extended outward. These

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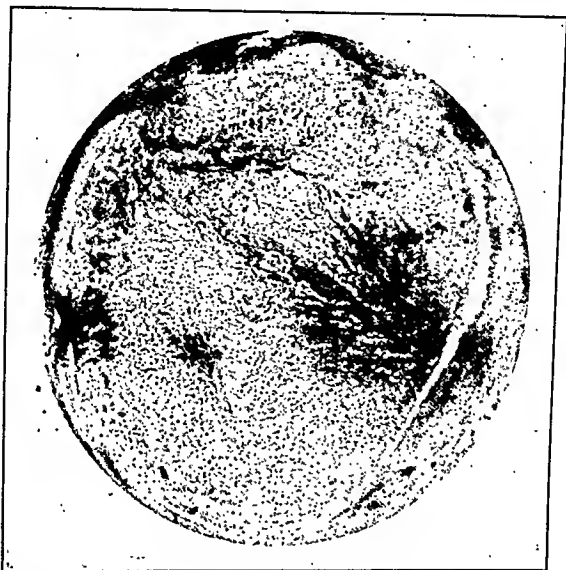


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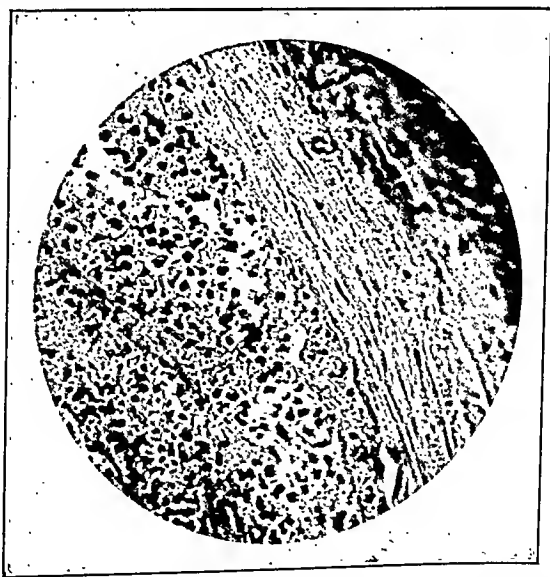


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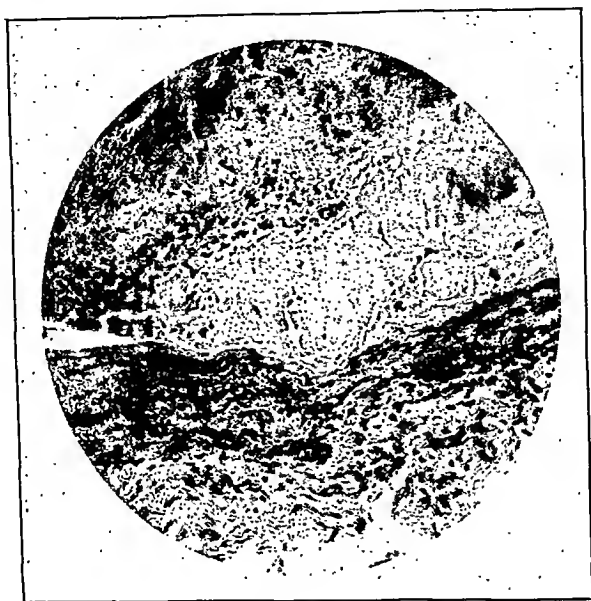


Fig. 10.—Section of same vein as shown in Fig. 9. (H. and E. stain  $\times 375$ .)

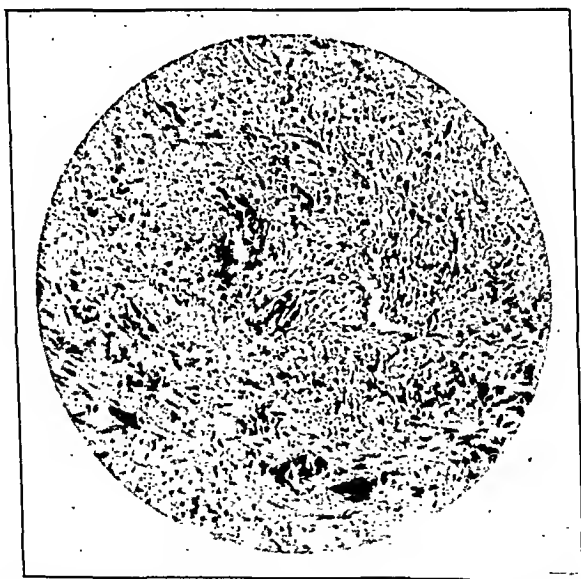


Fig. 11.—Photomicrograph of vein showing organization of a thrombus. 0.25 c.c. soricin, vein removed seventh day after injury. (H. and E. stain  $\times 375$ .)

to a tiny area on the vein wall was visible under the microscope. The vessel wall, even when no thrombus was seen, showed in some areas

were usually covered with platelets and white cells. This gave the thrombus a wavy, lacy appearance.

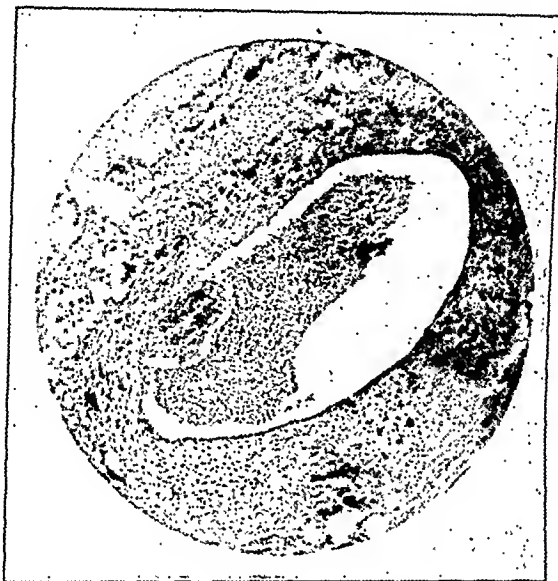


Fig. 8.—Photomicrograph of vein showing very small thrombus. 0.25 c.c. soricin, excised after twenty-four hours. (H. and E. stain  $\times 100$ .)



Fig. 9.—Photomicrograph of vein showing partial thrombosis. 0.15 c.c. soricin, heparin seventy-three hours, excised on seventh day. (H. and E. stain  $\times 45$ .)

In the heparinized veins, sections secured 60 to 72 hours after the injection of soricin showed, in those cases where there was no obstruc-

tion to blood flow, a complete freedom from thrombus formation in many instances. In others a small thrombus attached to a valve or

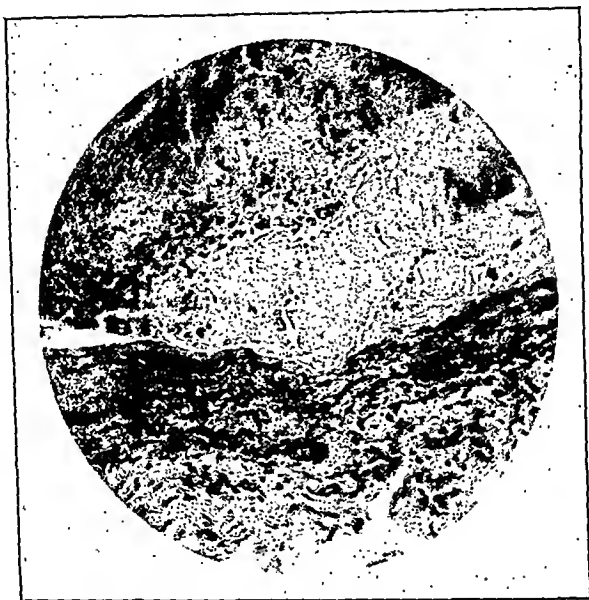


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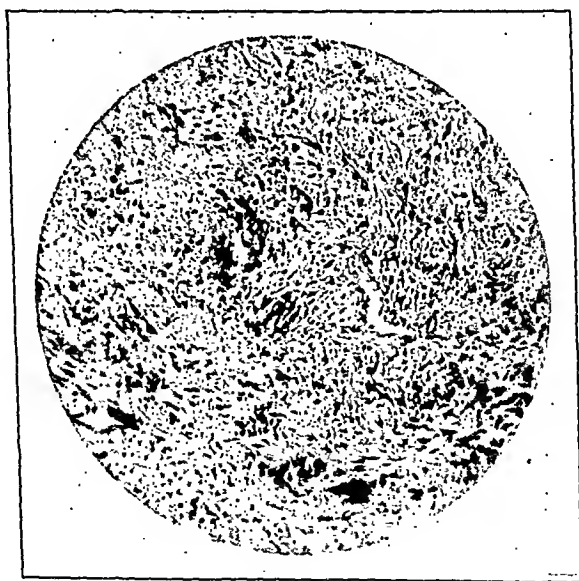


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signs of inflammatory reaction. The intima was usually normal although the nuclei seemed to be enlarged. The media usually showed an engorgement of capillaries and hemorrhage between the fibers. The nuclei of the cells of the media appeared broken or pyknotic. White blood cells were present in this layer and these were filled with dark-staining granules. The adventitia in a few cases showed signs of inflammatory reaction. The above findings were secured when the veins were removed 3 days after the injury. Six or 7 days after injury the vessel walls seemed to be largely free of inflammation but the cells of the intima were still rather hyperchromatic.

In the veins where a thrombus had formed there were definite signs of organization at the end of 6 days. The above points are illustrated in Figs. 4 to 11 inclusive.

#### DISCUSSION

The possibility that heparin might prevent thrombosis of blood vessels was appreciated by Howell and by many of the subsequent workers in this field. It has been shown by Mason<sup>13</sup> that heparin will prevent the intravascular clot produced by the injection of a potent solution of thrombokinase into the blood stream. Our investigations have differed from those which have preceded them in the following ways: (1) Thrombosis of veins was produced by mechanical and chemical injury to the intimal surface of the blood vessels. (2) In our more recent experiments a very highly potent and nontoxic preparation of heparin has been available in adequate quantities.

It has not previously been shown, to our knowledge, that heparin is capable of preventing the obstruction of blood vessels by thrombus and clot which form as a result of extensive injury. To accomplish this it is necessary, as we have shown, to keep the animal under the influence of heparin for prolonged periods. The heparin which was available when Mason conducted his very interesting experiments on the prevention of intravascular clotting by thrombokinase presumably had a potency of approximately 5 units per milligram. Some of our work has been conducted with heparin of a potency of 250 units per milligram, while more recently this has been of the order of 500 units per milligram. It is necessary to secure a high degree of purification if toxic products are to be eliminated. The administration of heparin of a potency of 250 units per milligram, in amounts effective in increasing the clotting time of the blood, for prolonged periods to human subjects is not a feasible procedure.

It should be appreciated that considerable care is required in conducting experiments in which the occlusion of veins is produced by mechanical injury. It is probable that if the veins of animals which were to receive heparin had been less severely injured than the controls, a large proportion of them would have failed to become occluded.

In our opinion, the heparinized veins were damaged quite as severely as the controls. If there was any difference in the extent of injury, we believe that the heparinized veins received the more severe traumatization.

There would seem to be less possibility of significant variation in the procedure used to injure the veins by chemical means. The soricin was injected under rigidly uniform conditions. While it is very interesting that the heparin was not effective in preventing occlusion of a larger proportion of the veins into which 0.25 c.c. of the soricin was injected, it would appear that there is a very significant difference between the numbers of the veins occluded in the control and test groups. Fifteen per cent of the control veins were patent, while 53 per cent of those which received heparin offered no obstruction to blood flow at the end of the experiment.

It is quite possible that if a larger series of veins had been studied with an injection of 0.15 c.c. of soricin that all of the heparinized veins would not have remained patent. The results were, however, remarkably uniform in a series of 24 veins studied. There was no obvious obstruction to blood flow in any of the 12 veins removed from animals which had received heparin. The small platelet thrombus in one of the veins was not detected before the vein was opened.

Very little further comment need be made on the nature of the obstructing mass in the vein. In many of the sections the platelets were easily demonstrable. In some cases the thrombus was composed almost entirely of platelets. It would appear that if heparinization is continued for approximately 70 hours, the intimal surfaces of the veins may heal sufficiently so that there is no danger of subsequent obstruction. In many cases the veins were removed from the animals seven days after the injury had been produced. At this time, in the obstructed vessels, the thrombus was usually firmly attached to the vein wall and showed definite evidence of organization. Recanalization might subsequently have taken place. In the vessels which were patent, the intima, in the gross, appeared normal. The microscopic findings have been described above.

It has been reported by Shionoya<sup>14</sup> that the administration of heparin does not prevent the formation of a white thrombus when the blood is made to pass through a collodion tube. It is possible, as Howell suggested, that large amounts of more highly purified heparin might affect this process. A study of this possibility is in progress in these laboratories.

The investigations on human cases were conducted merely to determine whether regional heparinization and general heparinization were feasible procedures with the preparations which were available. It has been shown (1) that no deleterious effects were produced in



signs of inflammatory reaction. The intima was usually normal although the nuclei seemed to be enlarged. The media usually showed an engorgement of capillaries and hemorrhage between the fibers. The nuclei of the cells of the media appeared broken or pyknotic. White blood cells were present in this layer and these were filled with dark-staining granules. The adventitia in a few cases showed signs of inflammatory reaction. The above findings were secured when the veins were removed 3 days after the injury. Six or 7 days after injury the vessel walls seemed to be largely free of inflammation but the cells of the intima were still rather hyperchromatic.

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the embolus had been removed, might give decisive results. If cases are available the effectiveness of purified heparin in these conditions will be tested.

The researches on heparin in this university were initiated in 1929 by one of us (C. H. B.) with two objectives in view. The first was to make adequate amounts of more highly purified material available for physiologic work; the second was to study the effect of the anticoagulant on thrombus formation. After some preliminary experiments with E. W. McHenry, the results of which showed that beef liver as well as dog liver was a useful source of the anticoagulant, the problem of the purification of heparin and the preparation of suitable quantities was undertaken by A. F. Charles, and D. A. Scott<sup>15</sup> in the Connaught Laboratories. These workers have made several reports on the results of their investigations. In their most recent paper they have described the method of preparation of a crystalline barium salt of heparin. This material consistently contains approximately 500 units per milligram. A sterile solution of this product after removal of most of the barium has been available for all of our recent investigations. We would like to acknowledge here the dependence of our work on the results obtained by Charles and Scott.

It is of great interest that Hedenius and Wilander,<sup>16</sup> using heparin prepared by a procedure elaborated by Charles and Scott in Toronto, have reported that the material exerts no deleterious effects in human subjects when administered intravenously in amounts which raised the clotting time well above the normal value. The effect of heparin on thrombosis was not studied, but Widström and Wilander<sup>17</sup> believe that they have demonstrated in experimental animals an inhibiting action of the anticoagulant on the formation of fibrin in pleural exudates.

#### SUMMARY AND CONCLUSIONS

1. The results of our experiments indicate that the incidence of obstruction of peripheral veins in dogs by thrombi formed as a result of certain mechanical or chemical injuries to the intimal surfaces of the blood vessels is definitely decreased when solutions of purified heparin are administered before and for prolonged periods following the injury. These findings are the results of observations on some three hundred veins.

2. The findings in the experiments in which injury was produced by chemical means suggest that the effect of heparin is clearly seen only under conditions in which the extent of the injury is just sufficient to produce thrombosis in most of the veins in animals which do not receive the anticoagulant. This statement refers to the absence of thrombus formation after heparin administration is discontinued. Thrombi have not been observed even after very severe chemical injury while the animal was well heparinized.

several cases in which regional heparinization was carried out with moderately pure heparin and (2) that using highly purified material prolonged general heparinization would appear to be feasible.

If the general heparinization of patients postoperatively proceeds as satisfactorily as at present, it is hoped that a large group can be studied. We appreciate fully that before any deductions concerning the results of this procedure on the incidence of thrombus formation can be drawn, a series consisting of at least several hundred cases must be studied. A statistical treatment of the clinical findings at present available on the frequency of vascular obstruction by thrombus may indicate that this number is grossly inadequate. Furthermore, it may not be feasible to administer heparin in an intravenous infusion of saline solution to patients for more than four or five days after operation. So little is known about the factors which cause thrombosis that it is difficult to decide whether or not this is an adequate period. The times at which embolism most frequently occurs do not provide the required information since heparinization would be directed against the formation of the potential embolus. The procedures used at present, which are directed toward prevention of (1) tissue injury (liberation of thrombokinase), (2) infection, and (3) stagnation of blood, are based on sound physiologic principles, but the results of their application cannot, as yet, be considered satisfactory. While the findings we have reported in experimental animals justify the inference that clinical thrombosis, attributable to certain etiologic factors, might be prevented by heparin, it is usually impossible to determine what factors are in operation in a particular clinical case. It should be borne in mind also that heparin has not been proved to be of physiologic significance. While information on its distribution in the body and mechanism of action is available, no direct evidence indicating a physiologic rôle has been obtained.

Under these circumstances clinical research may be advantageously conducted along at least two lines: (1) attempts to determine the cases in which thrombosis is likely to occur and (2) the administration, postoperatively, for prolonged periods of a solution of highly purified heparin which increases the clotting time of the blood but produces no deleterious effects.

It is probable that attempts favorably to influence the incidence of thrombosis in postoperative cases by the administration of heparin to as many patients as possible, is not the best method of determining whether or not the anticoagulant possesses any therapeutic value. The clinical condition characterized by recurrent multiple thromboses might, for example, present a better opportunity. The use of regional or general heparinization after embolectomy in suitable cases, i.e., those in which thrombus formation would be expected at the site from which

the embolus had been removed, might give decisive results. If cases are available the effectiveness of purified heparin in these conditions will be tested.

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It is of great interest that Hedenius and Wilander,<sup>16</sup> using heparin prepared by a procedure elaborated by Charles and Scott in Toronto, have reported that the material exerts no deleterious effects in human subjects when administered intravenously in amounts which raised the clotting time well above the normal value. The effect of heparin on thrombosis was not studied, but Widström and Wilander<sup>17</sup> believe that they have demonstrated in experimental animals an inhibiting action of the anticoagulant on the formation of fibrin in pleural exudates.

#### SUMMARY AND CONCLUSIONS

1. The results of our experiments indicate that the incidence of obstruction of peripheral veins in dogs by thrombi formed as a result of certain mechanical or chemical injuries to the intimal surfaces of the blood vessels is definitely decreased when solutions of purified heparin are administered before and for prolonged periods following the injury. These findings are the results of observations on some three hundred veins.

2. The findings in the experiments in which injury was produced by chemical means suggest that the effect of heparin is clearly seen only under conditions in which the extent of the injury is just sufficient to produce thrombosis in most of the veins in animals which do not receive the anticoagulant. This statement refers to the absence of thrombus formation after heparin administration is discontinued. Thrombi have not been observed even after very severe chemical injury while the animal was well heparinized.

3. While the intimal surfaces of veins, removed from heparinized animals several days after the injection of heparin has been discontinued, may appear on macroscopic examination to have recovered completely from the injury, microscopic studies may in some cases reveal minute masses of platelets filling small crevices in the intima.

4. The clotting time of the blood of the human subject may be increased by the intravenous administration of solutions of highly purified heparin. This procedure produces no deleterious effects even when the heparinization is maintained for as long as five days. General heparinization has now been carried out in seventy-six patients postoperatively.

5. The clotting time of the blood in one limb of the experimental animal or human subject may be increased by the intraarterial administration of heparin without affecting to more than a slight degree the clotting time of the blood in other parts of the body. This is only true when the rate of injection of heparin is relatively slow.

6. Various aspects of these results and some of the directions along which further investigations may proceed are discussed.

The Banting Foundation has generously supported this investigation by making grants at various times to two of us (D. W. G. M. and T. S. P.). The kindly interest of Professor W. E. Gallie, of the Department of Surgery, and Professor J. G. Fitzgerald, of the School of Hygiene, and the help in the histologic studies of Dr. D. L. MacLean are gratefully acknowledged. We are greatly indebted to Dr. O. M. Solandt for his help in some of the early experiments with sodium ricinoleate and to Dr. F. R. Wilkinson, who has made many of the recent observations on the effect of heparin on human subjects.

The expert technical assistance of Mr. Campbell Cowan has been of the greatest value.

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## ESOPHAGEAL DIVERTICULA

WITH A REPORT OF TEN CASES OF THE PULSION TYPE ORIGINATING  
IN THE PHARYNX

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### HISTORICAL

THE first description of a diverticulum of the esophagus was given by Ludlow in 1764, followed by later observations by Monroe in 1811, Bell in 1816, and Matthew Baille several years later. The earliest treatment was attempted dilatation of the obstructed esophagus by means of bougies. In 1848, Dendy attempted to obliterate diverticula by the use of caustics with no great success. Kluge in 1850 advocated extirpation of the sac, and Michoux in 1884 was the first to accomplish this. The first operation of this type in the United States was performed by Hearn, in 1896, but not reported until three years later. Geraid, of Berne, in 1896, after two fatal operative results, devised a technic of invaginating the sac without opening the esophagus. Ten years later, Barrow perfected a method which was the forerunner of our present-day technic in which he inserted a bougie into the pouch during the operation. This, of course, has now been replaced by the esophagoscope. His treatment of the sac was essentially the same as that now used. Since that time various operations for the treatment of esophageal or pharyngeal diverticula have been devised, all of which fall into two groups, one- or two-stage operations.

In 1910, C. H. Mayo<sup>1</sup> performed a two-stage method and claimed that in this way the possibility of a descending mediastinitis would be lessened.

Jackson and Gaub<sup>2</sup> in 1915 reported two cases successfully treated by a new one-stage method. This technic has been widely adopted since that time and is the procedure of choice with many surgeons. It has been used exclusively in our clinic.

Perfecting the two-stage procedure, Judd and Mayo<sup>3</sup> by 1920 had accumulated a series of fifty-four cases which they reported. Both one- and two-stage methods were used in these patients with only three deaths, two following a one-stage operation, and one after the two-stage procedure. There was one recurrence and one or two cases required postoperative dilatation with bougies.

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Received for publication, February 25, 1937.

Other surgeons, among them Lahey,<sup>4</sup> Pool,<sup>5</sup> Heyd,<sup>6</sup> and McEvers<sup>7</sup> have adopted and advocated the two-stage method. McEvers believes that postoperative esophageal dilatation is unnecessary. On the other hand, Lahey<sup>4</sup> feels that such treatment is frequently indicated to dilate the fibers of the cricopharyngeus, the constriction of which has to do with the production of the original lesion and which constriction is still present after operation.

Moynihan<sup>7</sup> in 1932 had operated on fifteen patients with esophageal diverticulum by the one-stage method with no complications and a perfect result in all cases. He strongly favored the one-stage operation and stated there was no reason why a competent surgeon with perfect technic should fear the dreaded complication of mediastinitis. Shallow<sup>8</sup> is of the opinion that pharyngeal diverticulum is a more proper name for the condition, since these pouches all really arise in the pharynx descending into the region of the upper esophagus as they increase in size. In support of this he reviews Killian's work on the anatomy of the pharynx and the possible sites of origin of these diverticula: (1) through a defect below the cricopharyngeus muscle, in the nature of a slit, through which pass the inferior branch of the recurrent laryngeal nerve, and a branch of the inferior thyroid artery; (2) above the cricopharyngeus muscle, on either the right or left side, more frequently on the left; (3) least frequently through the lowermost fibers of the inferior constricta muscle at a point pierced by another branch of the inferior thyroid artery.

Shallow<sup>8</sup> also reports seventy-six cases (85 per cent males and 15 per cent females) operated on by the one-stage method, with only two deaths, or a mortality of 2.6 per cent. One of his fatalities resulted from a diffuse pneumonia and the other from renal complications, the patient dying in uremia forty-eight hours after operation. He emphasizes the frequency of pulmonary complications and mentions as one factor that in many of these patients there is a pre-operative bronchitis resulting from a spilling of the contents of the sac into the larynx especially when the patient is asleep. Other complications were temporary pharyngeal fistulas in five of the early cases, which has not occurred with improvement in technic; and temporary postoperative hoarseness in two cases which subsequently cleared up. There were two recurrences in his series, one in a patient who had a double diverticulum, each portion of which was removed by a separate one-stage operation, six months apart, and the other in a patient past middle age with poorly developed pharyngeal musculature. Both were reoperated upon with no recurrence after ten and three years, respectively.

McQuillan<sup>9</sup> reported a case of recurrent diverticulum occurring after a two-stage operation, three months previously. At operation the recurrent sac was so large that excision was impossible, and the



procedure consisted in obliterating the sac by a multiple infolding or plication of its wall, which was very thin, contrary to the usual finding. Later x-ray examination of this patient showed a beginning diverticulum on the opposite (right) side.

Corlucci<sup>10</sup> also reports a recurrence in a patient who had had a one-stage operation five years previously.

Torek<sup>11</sup> states that recurrences can take place after all types of operations on the esophagus, but that they occur less frequently after the one-stage operation. He adds that the mortality in the one-stage procedure which, 30 years previously, was extremely high, has now been reduced almost to a minimum with the perfection of the technic.

The one-stage operation has been used exclusively at the hospital of the University of Pennsylvania with uniformly good results.

#### CASES OF ESOPHAGEAL DIVERTICULUM OPERATED UPON BY ELIASON AND TUCKER, 1922 TO 1934

This series is composed of ten cases operated upon during a twelve-year period, from 1922 to 1934, and is reported from the combined surgical service of E. L. Eliason and the bronchoscopic service of Gabriel Tucker at the hospital of the University of Pennsylvania.

Of the ten patients, seven were males, ranging in age from forty-two to seventy years, and three females, from sixty-five to sixty-eight years, the average age for the entire group being 58.5 years. From this it would seem that the condition is more frequent in males and occurs at an earlier age, except in one instance, in males.

The chief symptoms were those usually described in association with this condition, namely, dysphagia, regurgitation of liquids, and as the condition became worse, of solid food, always more marked when lying down, and cough. Hoarseness occurred in two cases, and in two there was marked weight loss. One patient complained of a burning sensation in the pharynx. The duration of symptoms varied considerably, the longest period being fifteen years, and the shortest four months, with an average length of time of four years. In only one was there palpable fullness of the lower neck, and in this case pressure over this area produced a gurgling sound. The Boyce sign of pulsion diverticulum was positive in each case.

All patients were examined roentgenologically with both films and fluoroscopic study with and without an opaque mixture in order to establish the location and size of the pouch. Esophagoscopic examination was made of the pouch and the hypopharynx to exclude ulceration either benign or malignant. The patient was then given a string to swallow. When this had passed far enough into the small bowel to be firmly anchored when pulled upon, it was used as a guide to find the orifice of the subdiverticular esophagus. The opening into the subdiverticular esophagus is just in front of the neck of the pouch,

and it is very difficult to find in many cases. The esophagoscope was passed over the taut string and the opening of the esophagus in the pharynx and the entire subdiverticular esophagus were carefully examined to exclude ulceration, stricture, or other intrinsic lesions. These examinations are routine in every case and definitely establish the diagnosis and give an impression of size, character, and location of the diverticulum and reveal or exclude evidences of other disease of the esophagus which might be an important consideration in connection with the operative procedure.

The anesthesia employed in the first five cases was ether by intratracheal administration, and in the last five, avertin, and local, which has proved more satisfactory.

A one-stage operation was performed in all of these cases with the aid of the esophagoscope, using the technic devised by Jackson and Gaub.

In one case, because of the very large size of the pouch and its pressure on the subdiverticular esophagus, the patient was unable to take liquids in sufficient quantity for proper nourishment and came into the hospital in very poor general condition. In this case a string was swallowed, the esophagoscope passed over the swallowed string, and a feeding tube put in the stomach. The esophagoscope was removed leaving the tube and string in position and the upper end of the feeding tube was brought through the pharynx and anterior nares. The string and feeding tube were allowed to remain in the esophagus for several weeks until the patient's general condition became such as to justify operative excision of the diverticulum. At the time esophagoscopy was given during the excision of the diverticulum, the feeding tube was allowed to remain in position, and it was found that it was much easier to enter the subdiverticular esophagus over the string with the feeding tube already placed. Also during withdrawal of the esophagoscope, the site of excision and inversion of the neck of the sac in the pharynx could be inspected satisfactorily with the esophagoscope. This led us to modify the procedure as follows:

#### THE IMPROVED PROCEDURE OF ESOPHAGOSCOPIC AID

After x-ray study with both films and fluoroscopy with the use of an opaque mixture the patient is given a No. 14 twisted silk thread with a frayed end, fifteen feet in length. The end of the string is swallowed slowly with small amounts of water until thirteen feet have entered the esophagus. This should consume about a thirty-six-hour period. The remaining two feet are then anchored outside the mouth so that the string cannot be completely swallowed and after forty-eight hours have elapsed the esophagoscopy examination is made. The esophagoscope is first passed into the pharynx and the

diverticular pouch is carefully examined. Usually a considerable quantity of retained food is evacuated in order to inspect the interior of the pouch. The esophagoscope is then withdrawn and passed over the string which is pulled taut and followed as a guide into the entrance of the subdiverticular esophagus. The entire esophagus is carefully examined and a feeding tube, No. 14 Levin, is passed through the esophagoscope alongside the string. The esophagoscope is withdrawn leaving the string and feeding tube in position, and the upper end of the feeding tube is brought out through the nose where it remains until after the operative procedure of excision of the sac. The string is fastened outside the mouth so it will not be completely swallowed.

#### ESOPHAGOSCOPIC AID DURING EXCISION OF THE POUCH

After external incision in the neck and exposure of the pouch by the surgeon, the esophagoscope, 8 mm. full lumen by 45 cm., is introduced into the pharynx and the pharynx and pouch are emptied. Under the guidance of the surgeon from the wound in the neck, the pouch is carried gently outward until it is visible in the open wound. Transillumination with the esophagoscope will show the limits of the pouch. The bottom of the pouch is grasped with an Allis type forceps by the surgeon and pulled outward and separated from the esophagus. The esophagoscope is withdrawn as the pouch is pulled outward until the neck of the diverticulum is reached. Then the esophagoscope is entirely withdrawn and threaded over the previously swallowed string and reintroduced with the string as a guide avoiding the location of the diverticular pouch. The string is followed alongside of the feeding tube, which has remained in position and which also assists in the passage of the esophagoscope into the subdiverticular esophagus. The sac is then withdrawn into the wound by the surgeon who excises enough to eliminate the pouch formation. The neck of the sac is inverted or excised as the surgeon may desire. The esophagoscope in the subdiverticular esophagus prevents excision of too great an amount of the redundant esophagus in the neighborhood of the pouch. After the sac is removed, the string is cut and pushed into or withdrawn from the stomach and the esophagus at the site of the excision of the pouch is carefully inspected as the tube is removed. The feeding tube remains in place.

The advantages of the modified esophagoscopic technic are: first, the feeding tube assists in getting the esophagoscope into the subdiverticular esophagus and; second, the site of excision of the diverticulum is inspected as the esophagoscope is withdrawn.

The technic is as follows: After exposure of the sac by means of an incision along the anterior border of the left sternocleidomastoid

muscle (all of the diverticula presented to the left, as is usually the case), the esophagoscope was then inserted into the hypopharynx and pouch thus facilitating its dissection and immobilization and preventing the dissection from being carried too far. It was necessary to ligate the inferior thyroid artery in one instance. Shallow<sup>s</sup> found this procedure necessary in 35 per cent of his cases, one double diverticulum being caused by the presence of the artery. The esophagoscope was then withdrawn and introduced over the previously swallowed string into the subdiverticular esophagus. The sac was crushed about a centimeter from its base using a small Payr clamp and the excess removed by means of the actual cautery passed along the distal edge of the clamp. The stump was then inverted by from three to five rows of interrupted mattress sutures of fine chromic catgut. In no instance did esophageal obstruction result. The fascia and skin were then closed in layers in an appropriate manner. In two cases the sac was quite small and simple inversion without excision of the pouch was carried out, since it was apparent that no obstruction would result. The feeding tube was allowed to remain in position for purposes of feeding during the first few postoperative days. Drainage was employed in all cases, using the cigarette or Penrose type of drain. The wounds closed promptly after removal of the drains on the third to fifth postoperative day, except in one case, in which there was persistent foul discharge for ten days but subsequent satisfactory healing. The skin sutures were removed usually on the fifth or sixth postoperative day.

The postoperative treatment in these cases consisted in administration of an adequate liquid diet of high caloric value for seven to ten days, the last three or four days of which period part of the liquids were given by mouth, if well tolerated, in gradually increasing amounts. The tube was removed on the eighth to tenth day and soft diet allowed. The patients were usually allowed out of bed on the eleventh to fifteenth day, depending on their general condition and the degree of healing of the wound, and discharged one or two days later.

No evidence of malignancy in any of the diverticula could be found at the esophagosopic examination or later by the pathologist. Shallow<sup>s</sup> reports one such case. Nine of these patients lived and there was one death, giving a mortality of 10 per cent.

The one death occurred in the case of a woman sixty-eight years of age who developed atelectasis thirty-six hours after operation and later pneumonia, and who died on the fifth postoperative day, despite adequate oxygen therapy, nourishment by Jutte tube, respiratory exercises, and circulatory stimulants. At postmortem examination there was found atelectasis of the lower lobe of the left lung, lobar

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The technique is as follows: After exposure of the sac by means of an incision along the anterior border of the left sternocleidomastoid

## SUMMARY AND CONCLUSIONS

1. A series of ten cases of esophageal diverticulum operated upon by the one-stage method is reported in which there was one death, or a mortality of 10 per cent.

2. The majority of the patients were males, and with one exception, the condition occurred at an earlier age in the ten males than in the three females.

3. The chief symptoms of the condition are dysphagia, regurgitation, and cough.

4. Diagnosis of esophageal diverticulum should be confirmed preoperatively by films and fluoroscopic study with an opaque mixture and by esophagoscopy examination.

5. The procedure of choice is the one-stage operation with the aid of the esophagoscope, anesthesia being avertin and local.

6. In none of the patients did a mediastinitis occur.

7. Eight of the nine patients who recovered have been followed and seven of these are perfectly well, or were, when last heard from. There has been a probable recurrence in one case.

8. Postoperative bouginage was not required in any case.

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pneumonia of the right upper lobe, and bronchopneumonia of the right lower lobe. The examination was limited to examination of the thorax through an abdominal incision and hence the operative site could not be inspected.

Other complications in this series were: persistent drainage from the operative site in one case as mentioned; paroxysmal auricular fibrillation in one case, controlled by digitalis; and temporary paralysis of the left vocal cord, secondary to injury of the left recurrent laryngeal nerve, in two cases. One of these cleared up before the patient left the hospital and the other soon after discharge. In none of the patients did a mediastinitis occur.

TABLE SHOWING COMPLICATIONS

Prolonged drainage	1
Auricular fibrillation	1
Temporary paralysis of vocal cord	2

The temporary paralysis of the vocal cord was due to stretching of the recurrent nerve on the left side during the operation and was completely recovered within one month of the operation in each case.

#### FOLLOW-UP

The end-results in the majority of these nine patients who recovered from operation were quite satisfactory.

Two patients were followed for four months and six months respectively and both were entirely symptom-free at the end of these periods; neither returned for subsequent visits nor can they be reached by letter.

One patient was completely relieved for one year after operation and since then was not heard from until a recent reply to a questionnaire. In this he states that there was a recurrence of symptoms after the first year and that he has continued to suffer some degree of discomfort. This cannot be taken as conclusive evidence of a failure, since the patient was not personally seen and examined.

Five patients have been followed for periods of from one to six years and all are perfectly well, most of them showing marked weight gain in addition to relief of all symptoms.

One patient did not return for follow-up examination and no information can be obtained concerning him.

TABLE SHOWING END-RESULTS

Completely cured, less than one year	2
Completely cured, one to six years	5
Cured for one year, probable recurrence	1
No follow-up	1
Death	1

In some animals perforation was accomplished by means of a sharp brass pipe passed through the esophagus. After the induction of anesthesia, a sterilized rubber tube was passed perorally into the stomach which was then perforated by a sterilized, sharpened, metal pipe passed through the rubber tube (Fig. 1). Such perforations occurred at the greater curvature. When it was desired to permit an easy escape of stomach contents into the peritoneal cavity, a pipe with numerous, fairly large openings in its wall was used (Fig. 2). Studies by Borman and Bergh have demonstrated that when the latter type of pipe is used, fluid contents of the stomach invariably escape into the peritoneal cavity and pneumoperitoneum sometimes results, while there is practically no escape when the solid-walled pipe is used.

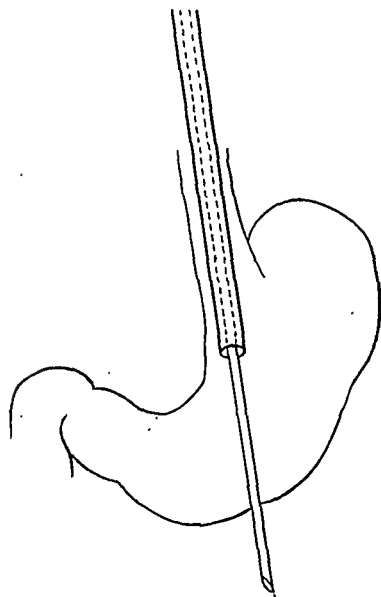


Fig. 1.

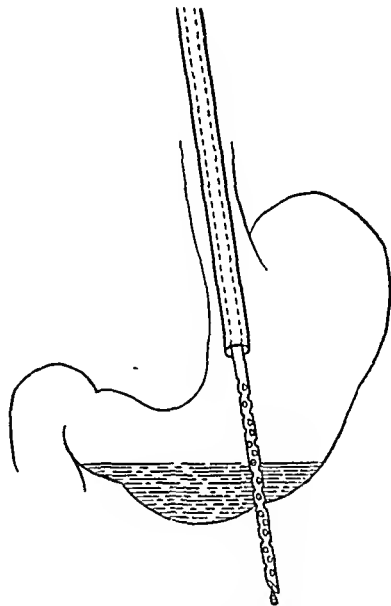


Fig. 2.

Fig. 1.—Method of perforating the stomach with a solid-walled pipe without performing laparotomy.

Fig. 2.—Method of perforating the stomach with a pipe which allows stomach contents to escape.

In some animals an attempt was made to simulate the edema and inflammatory changes which exist around peptic ulcers by the preliminary injection of a sclerosing solution (proliferol). One to three cubic centimeters of the sclerosing solution were injected into the antral wall and the viscus was perforated through this area several days later.

In studying intestinal perforations, we used fasted animals exclusively, the period of starvation ranging from one to three days. Most perforations consisted of an unsutured incision one centimeter in length in the axis of the bowel along the antimesenteric border. Transverse incisions were made in some cases, but the results did not differ from the others.



# PERFORATION OF THE GASTROINTESTINAL TRACT: AN EXPERIMENTAL STUDY OF FACTORS INFLUENCING THE DEVELOPMENT OF PERITONITIS\*

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**P**ERFORATION of the gastrointestinal tract following trauma or as a result of pathologic processes originating within the digestive canal is encountered frequently in clinical medicine and surgery. The seriousness of such an accident is well known.

The observation that fasting animals withstand experimental perforation better than animals which recently have taken food stimulated us to undertake a study of some of the factors influencing the development of peritonitis following perforation.

Soiling of the peritoneal cavity follows the escape of the contents of the stomach or intestine and, in accordance with the general bacteriologic rule, the degree of infection which will occur under such circumstances depends upon the number and virulence of the escaping organisms and upon the local and general resistance of the host.

The number of organisms escaping is influenced by several factors: the size of the perforation, the length of time it remains open, and the forces tending to carry contents of the viscus out into the peritoneal cavity are important, as well as the number of viable, pathogenic bacteria and the amount and fluidity of material present in the viscus at the level of perforation. Factors influencing the virulence of microorganisms are not well understood.

Factors influencing the general resistance of the host are likewise complex. Local resistance, however, may be affected by the juices escaping from the intestinal tract.

## METHOD

Under pentobarbital-sodium anesthesia and with aseptic precautions, perforations were established at various levels of the gastrointestinal tract of laboratory animals after periods of fasting and also following the ingestion of food. A total of one hundred and forty-five animals were used.

Most of the perforations of the stomach consisted of unsutured linear incisions one centimeter in length, but in a few cases a circular defect was made. As indicated in the tables, the incisions were made in various regions of the viscus.

\*Aided by a grant from the Research Funds of the Graduate School, University of Minnesota.

Received for publication, March 8, 1937.

tion closed itself almost immediately and within twenty-four hours was well sealed by fibrinous exudate. In the earliest experiments water was withheld for twenty-four hours and food for forty-eight hours, but in later studies the animals were allowed to take food and water at will without ill effects.

There appeared to be no relationship between the location of the perforation in the stomach wall and the development of peritonitis. The type of perforation was likewise unimportant unless a large defect were made, in which case spontaneous closure of the opening would be less likely to occur.

II. Perforation of the stomach containing food was performed in thirty animals—thirteen dogs, five cats, ten rabbits, and two guinea pigs (Table II). In this series there were twenty-six deaths from

TABLE II  
PERFORATION OF STOMACH CONTAINING FOOD BY MEANS OF AN INCISION 1 CM. IN LENGTH IN THE ANTERIOR WALL (MORTALITY 86.7%)

ANIMAL	FATE	BACTERIOLOGY	REMARKS
Dog 30	Survived		Sacrificed. No peritonitis
31	Died 24 hr.	<i>B. subtilis</i> and <i>B. welchii</i>	Generalized peritonitis
32	Died 24 hr.		Generalized peritonitis
33	Died 24 hr.	Gm. + rods, cocci, and streptococci	Perforation open
34	Died 96 hr.	Gm. - rods	Generalized peritonitis
		Gm. + rods and streptococci	Generalized peritonitis
35	Died 24 hr.	Gm. - rods	Generalized peritonitis
36	Died 24 hr.	Same organisms	Generalized peritonitis
37	Died 72 hr.	Same organisms	Generalized peritonitis
38	Died 24 hr.	Same organisms	Generalized peritonitis
39	Died 48 hr.	Same organisms	Generalized peritonitis
40	Died 24 hr.	Same organisms	Generalized peritonitis
41	Died 24 hr.	Gm. + and Gm. - rods	Generalized peritonitis
42	Died 24 hr.	Gm. + rods, diplococci, and staphylococci	Generalized peritonitis
Cat 43	Died 24 hr.	Gm. + rods, streptococci, and Gm. - rods	Parasites extruding
44	Died 24 hr.	Gm. + rods and streptococci	Generalized peritonitis
45	Died 48 hr.	Gm. + and Gm. - rods	Generalized peritonitis
46	Died 9 days	Gm. + anaerobes, rods, and streptococci	Generalized peritonitis
47	Died 24 hr.	Gm. + anaerobes, rods, and streptococci	Generalized peritonitis
Rabbit 48	Survived		Gastrojejunal fistula
49	Survived		Perforation healed
50	Died 24 hr.		Generalized peritonitis
51	Died 24 hr.		Generalized peritonitis
52	Died 24 hr.		Generalized peritonitis
53	Died 24 hr.		Generalized peritonitis
54	Died 24 hr.		Generalized peritonitis
55	Died 24 hr.		Generalized peritonitis
56	Died 24 hr.		Generalized peritonitis
57	Died 5 days		Generalized peritonitis
Guinea pig 58	Died 3 days		Generalized peritonitis
59	Survived		Sealed by omentum. No peritonitis

All animals were observed for signs of peritonitis and those which died were subjected to autopsy. Many of the surviving animals were sacrificed or operated upon to observe the healing process. Bacteriologic studies were made in cases in which peritonitis developed.

## RESULTS

I. Perforation of the empty stomach was carried out in twenty-nine animals. In this series there were two deaths from peritonitis, a mortality of 6.9 per cent (Table I). In one of the two fatal cases a large

TABLE I  
PERFORATION OF EMPTY STOMACH (MORTALITY 6.9%)

ANIMAL	FATE	TYPE OF PERFORATION	REMARKS
Dog 1	Survived	1 cm. incision in anterior wall	No water for 24 hr.; no food for 48 hr. Sacrificed in 12 days. Healed. No peritonitis
2	Survived	1 cm. incision in anterior wall	Same regime. Sacrificed in 4 days. No peritonitis
3	Survived	1 cm. incision in anterior wall	Food and water at will. Sacrificed in 6 days. No peritonitis.
4	Survived	1 cm. incision in anterior wall	Same regime. Sealed in 48 hr.
5	Survived	1 cm. incision in anterior wall	Same regime. Sealed in 24 hr.
6	Survived	1 cm. incision in anterior wall	Same regime. Sealed in 3 days
7	Survived	1 cm. incision in anterior wall	Not sacrificed
8	Survived	1 cm. incision in anterior wall	Sacrificed in 5 days. Healed
9	Survived	1 cm. incision in anterior wall	Not sacrificed
10	Survived	1 cm. incision in anterior wall	Not sacrificed
11	Died 72 hr.	1 cm. incision in anterior wall	Perforation not healed. Generalized peritonitis. Gram + streptococci, staphylococci, and rods
12	Survived	1 cm. incision in anterior wall	Not sacrificed
13	Survived	1 cm. incision in anterior wall	Not sacrificed
14	Survived	1 cm. incision in fundus	Not sacrificed
15	Survived	1 cm. incision in fundus	Not sacrificed
16	Survived	1 cm. incision in fundus	Not sacrificed
17	Survived	1 cm. incision in fundus	Not sacrificed
18	Survived	1 cm. incision in posterior wall	Not sacrificed
19	Survived	1 cm. incision in posterior wall	Not sacrificed
20	Survived	1 cm. incision in posterior wall	Not sacrificed
21	Survived	1 cm. incision in posterior wall	Not sacrificed
22	Survived	Circular defect, 0.5 cm. diameter	Not sacrificed
23	Survived	Circular defect, 0.5 cm. diameter	Not sacrificed
24	Died 24 hr.	Circular defect, 1.5 cm. diameter	Perforation open. Severe peritonitis. Gram + rods and streptococci
25	Survived	Sharpened pipe—solid walled	Examination in one week. Perforation healed. No peritonitis
26	Survived	Sharpened pipe—solid walled	Same. No peritonitis
27	Survived	Sharpened pipe—solid walled	Same. No peritonitis
Cat 28	Survived	1 cm. incision in anterior wall	Not sacrificed
29	Survived	1 cm. incision in anterior wall	Not sacrificed

circular defect (1.5 cm.) had been established, and in the other the linear perforation had remained open. In the remaining animals the perfora-

tion closed itself almost immediately and within twenty-four hours was well sealed by fibrinous exudate. In the earliest experiments water was withheld for twenty-four hours and food for forty-eight hours, but in later studies the animals were allowed to take food and water at will without ill effects.

There appeared to be no relationship between the location of the perforation in the stomach wall and the development of peritonitis. The type of perforation was likewise unimportant unless a large defect were made, in which case spontaneous closure of the opening would be less likely to occur.

II. Perforation of the stomach containing food was performed in thirty animals—thirteen dogs, five cats, ten rabbits, and two guinea pigs (Table II). In this series there were twenty-six deaths from

TABLE II

PERFORATION OF STOMACH CONTAINING FOOD BY MEANS OF AN INCISION 1 CM. IN LENGTH IN THE ANTERIOR WALL (MORTALITY 86.7%)

ANIMAL	FATE	BACTERIOLOGY	REMARKS
Dog 30	Survived		Sacrificed. No peritonitis
31	Died 24 hr.	<i>B. subtilis</i> and <i>B. welchii</i>	Generalized peritonitis
32	Died 24 hr.		Generalized peritonitis
33	Died 24 hr.	Gm. + rods, cocci, and streptococci	Perforation open
		Gm. - rods	Generalized peritonitis
34	Died 96 hr.	Gm. + rods and streptococci	Generalized peritonitis
		Gm. - rods	
35	Died 24 hr.	Same organisms	Generalized peritonitis
36	Died 24 hr.	Same organisms	Generalized peritonitis
37	Died 72 hr.	Same organisms	Generalized peritonitis
38	Died 24 hr.	Same organisms	Generalized peritonitis
39	Died 48 hr.	Same organisms	Generalized peritonitis
40	Died 24 hr.	Same organisms	Generalized peritonitis
41	Died 24 hr.	Gm. + and Gm. - rods	Generalized peritonitis
42	Died 24 hr.	Gm. + rods, diplococci, and staphylococci	Generalized peritonitis
Cat 43	Died 24 hr.	Gm. + rods, streptococci, and Gm. - rods	Parasites extruding
44	Died 24 hr.	Gm. + rods and streptococci	Generalized peritonitis
45	Died 48 hr.	Gm. + and Gm. - rods	Generalized peritonitis
46	Died 9 days	Gm. + anaerobes, rods, and streptococci	Generalized peritonitis
47	Died 24 hr.	Gm. + anaerobes, rods, and streptococci	Generalized peritonitis
Rabbit 48	Survived		Gastrojejunal fistula
49	Survived		Perforation healed
50	Died 24 hr.		Generalized peritonitis
51	Died 24 hr.		Generalized peritonitis
52	Died 24 hr.		Generalized peritonitis
53	Died 24 hr.		Generalized peritonitis
54	Died 24 hr.		Generalized peritonitis
55	Died 24 hr.		Generalized peritonitis
56	Died 24 hr.		Generalized peritonitis
57	Died 5 days		Generalized peritonitis
Guinea pig 58	Died 3 days		Generalized peritonitis
59	Survived		Sealed by omentum. No peritonitis

peritonitis, a mortality of 86.7 per cent. Only one of the thirteen dogs survived, and nine of the twelve deaths occurred within twenty-four hours after the perforation. The rabbit's stomach was found to contain ingesta even after prolonged periods of fasting. Eight of the ten rabbits died from peritonitis. One of the survivors developed a spontaneous gastrojejunal fistula at the point of perforation, and in the other the perforation was sealed by omentum. Fatal peritonitis developed in all five cats and in one of the guinea pigs.

Bacteriologic studies of the peritoneal exudate revealed the presence of a variety of organisms (Table II).

III. Perforation of the stomach of fasting dogs immediately before and after the administration of liquids was carried out in seventeen animals, with three deaths from peritonitis, a mortality of 17.6 per cent (Table III). Except when the anesthesia was light, allowing the animal to strain, minimal amounts of the liquid escaped into the peritoneal cavity. The intragastric tension did not increase in proportion to the

TABLE III

PERFORATION OF STOMACH OF FASTING DOGS IMMEDIATELY BEFORE AND AFTER THE ADMINISTRATION OF LIQUIDS (MORTALITY 17.6%)

DOG	FATE	PROCEDURE	REMARKS
60	Survived	Drank 100 c.c. milk—perforated—stomach aspirated	No peritonitis
61	Survived	Drank 100 c.c. milk—perforated—stomach aspirated	No peritonitis
62	Survived	Drank 100 c.c. milk—perforated—stomach aspirated	No peritonitis
63	Survived	Drank 100 c.c. milk—perforated—stomach aspirated	No peritonitis
64	Died 24 hr.	Perforated—200 c.c. water instilled	Generalized peritonitis— Gm. + rods, diplococci, and staphylococci and Gm. - rods
65	Survived	Perforated—200 c.c. water instilled	No peritonitis
66	Survived	Perforated—200 c.c. water instilled	No peritonitis
67	Survived	Drank 200 c.c. milk—perforated— not aspirated	No peritonitis
68	Survived	Drank 200 c.c. milk—perforated— not aspirated	No peritonitis
69	Survived	Drank 200 c.c. milk—perforated— not aspirated	No peritonitis
70	Survived	Drank 200 c.c. milk—perforated— not aspirated	No peritonitis
71	Died 24 hr.	Given 500 c.c. milk—perforated— not aspirated	Generalized peritonitis
72	Survived	Given 500 c.c. milk—perforated— not aspirated	No peritonitis
73	Survived	Given 500 c.c. milk—perforated— not aspirated	No peritonitis
74	Died 24 hr.	Given 500 c.c. milk plus barium— perforated—not aspirated	Generalized peritonitis— Gm. + rods, streptococci, and diplococci and Gm. - rods
75	Survived	Given 500 c.c. milk plus barium— perforated—not aspirated	No peritonitis
76	Survived	Given 500 c.c. milk plus barium— perforated—not aspirated	No peritonitis

amount of liquid administered, since the stomach walls are able to accommodate themselves to the volume of gastric contents without increasing the pressure. Straining, however, did increase the intragastric tension sufficiently to force fluid from the stomach into the peritoneal cavity. Peristalsis did not cause stomach contents to be forced out through the perforation.

The perforation in dogs 60 to 70 was carried out by means of the metal pipe with openings in its wall (Fig. 2). The others were perforated by means of an unsutured linear incision. The first method permits x-ray examination for pneumoperitoneum, but when laparotomy has been carried out the presence of gas in the peritoneal cavity is without significance.

IV. Perforation of the empty stomach through an area previously injected with a sclerosing solution was carried out in ten dogs (Table IV). Four of these animals died from peritonitis, a 40 per cent mortal-

TABLE IV  
PERFORATION OF EMPTY STOMACH OF THE DOG. PROLIFEROL INJECTED  
INTO WALL (MORTALITY 40%)

DOG	AMOUNT INJECTED	INTERVAL BEFORE PERFORA- TION	FATE	BACTERIOLOGY	REMARKS
77	2 c.c.	3 days	Survived		
78	2 c.c.	3 days	Survived		
79	1 c.c.	3 days	Survived		
80	2 c.c.	3 days	Survived		
81	2 c.c.	5 days	Survived		
82	2 c.c.	30 days	Survived		
83	2 c.c.	5 days	Died 24 hr.	Gm. + rods and cocci, and Gm. - rods	Very little induration Generalized peritonitis.
84	3 c.c.	3 days	Died 6 days	Mixed organisms	Perforation open Generalized peritonitis.
85	1 c.c.	3 days	Died 7 days	Mixed organisms	Perforation open Generalized peritonitis.
86	2 c.c.	5 days	Died 6 wk.	Gm. + rods, streptococci, and spore formers, and Gm. - rods	Perforation open Exudate over perforation. Much free fluid in the peritoneal cavity. Low grade peritonitis

ity. Autopsies revealed that the perforations had failed to heal in the fatal cases. There was no definite correlation between the amount of solution injected or the interval elapsing before perforation and the mortality rate. The edema and infiltration produced by the injection is the closest experimental approach to the conditions existing in the presence of peptic ulcer.

V. Perforation of the duodenum was established in sixteen dogs, with a mortality of 81.2 per cent from peritonitis (Table V). In twelve an-

peritonitis, a mortality of 86.7 per cent. Only one of the thirteen dogs survived, and nine of the twelve deaths occurred within twenty-four hours after the perforation. The rabbit's stomach was found to contain ingesta even after prolonged periods of fasting. Eight of the ten rabbits died from peritonitis. One of the survivors developed a spontaneous gastrojejunal fistula at the point of perforation, and in the other the perforation was sealed by omentum. Fatal peritonitis developed in all five cats and in one of the guinea pigs.

Bacteriologic studies of the peritoneal exudate revealed the presence of a variety of organisms (Table II).

III. Perforation of the stomach of fasting dogs immediately before and after the administration of liquids was carried out in seventeen animals, with three deaths from peritonitis, a mortality of 17.6 per cent (Table III). Except when the anesthesia was light, allowing the animal to strain, minimal amounts of the liquid escaped into the peritoneal cavity. The intragastric tension did not increase in proportion to the

TABLE III

PERFORATION OF STOMACH OF FASTING DOGS IMMEDIATELY BEFORE AND AFTER THE ADMINISTRATION OF LIQUIDS (MORTALITY 17.6%)

DOG	FATE	PROCEDURE	REMARKS
60	Survived	Drank 100 c.c. milk—perforated—stomach aspirated	No peritonitis
61	Survived	Drank 100 c.c. milk—perforated—stomach aspirated	No peritonitis
62	Survived	Drank 100 c.c. milk—perforated—stomach aspirated	No peritonitis
63	Survived	Drank 100 c.c. milk—perforated—stomach aspirated	No peritonitis
64	Died 24 hr.	Perforated—200 c.c. water instilled	Generalized peritonitis—Gm. + rods, diplococci, and staphylococci and Gm. - rods
65	Survived	Perforated—200 c.c. water instilled	No peritonitis
66	Survived	Perforated—200 c.c. water instilled	No peritonitis
67	Survived	Drank 200 c.c. milk—perforated— not aspirated	No peritonitis
68	Survived	Drank 200 c.c. milk—perforated— not aspirated	No peritonitis
69	Survived	Drank 200 c.c. milk—perforated— not aspirated	No peritonitis
70	Survived	Drank 200 c.c. milk—perforated— not aspirated	No peritonitis
71	Died 24 hr.	Given 500 c.c. milk—perforated— not aspirated	Generalized peritonitis
72	Survived	Given 500 c.c. milk—perforated— not aspirated	No peritonitis
73	Survived	Given 500 c.c. milk—perforated— not aspirated	No peritonitis
74	Died 24 hr.	Given 500 c.c. milk plus barium— perforated—not aspirated	Generalized peritonitis— Gm. + rods, streptococci, and diplococci and Gm. - rods
75	Survived	Given 500 c.c. milk plus barium— perforated—not aspirated	No peritonitis
76	Survived	Given 500 c.c. milk plus barium— perforated—not aspirated	No peritonitis

TABLE VI  
PERFORATION OF JEJUNUM OF DOG  
(FASTING ANIMALS)  
(MORTALITY 44.4%)

DOG	DISTANCE FROM THE DUODENO- JEJUNAL ANGLE	FATE	BACTERIOLOGY	REMARKS
103	15 cm.	Died 48 hr.	Gm. + diplococci, rods, and Gm. - rods	Perforation open Generalized peritonitis
104	45 cm.	Died 24 hr.	Gm. + and Gm. - rods	Perforation open Generalized peritonitis
105	45 cm.	Survived		
106	60 cm.	Survived		
107	60 cm.	Died 24 hr.	Gm. + spore formers, rods, streptococci, and Gm. - rods	Perforation open Generalized peritonitis
108	60 cm.	Survived		
109	75 cm.	Died 24 hr.	Gm. + spore formers, rods, and streptococci, and Gm. - rods	Perforation open Generalized peritonitis
110	90 cm.	Survived		
111	90 cm.	Survived		

perforated. At the time of reoperation, however, no ulcers were found. The jejunum was, therefore, perforated by a linear incision just distal to the anastomosis (fasting animals). The animals all survived jejunal perforation, and one animal was so perforated on three occasions. Two of the animals subsequently died of spontaneous perforation of jejunal ulcers following a meal.

VII. Perforation of the lower ileum was performed in nine dogs (Table VIII). All of these animals died from peritonitis within seventy-

TABLE VII  
JEJUNAL PERFORATION IN EXALTO-MANN-WILLIAMSON DOGS  
BEYOND GASTROJEJUNAL ANASTOMOSIS  
(FASTING ANIMALS)  
(MORTALITY 0%)

DOG	FATE	REMARKS
112	Survived	No ulcer at 1 month. Jejunum incised at 1 month. Healed. Three weeks later dog died of spontaneous perforation of jejunal ulcer.
113	Survived	Jejunum incised at 1 month, 3 months, and 5 months. Healed each time. No ulcer developed during period of observation.
114	Survived	Jejunum incised at 3 weeks. No peritonitis. Animal died three months later of spontaneous perforation of a jejunal ulcer.

two hours, a mortality of 100 per cent. Autopsy revealed that the perforation had remained open in every case.

VIII. Perforation of the large bowel was carried out at three levels: the cecum, descending colon, and rectum.



TABLE V  
PERFORATION OF DUODENUM OF DOG  
(FASTING ANIMALS)  
(MORTALITY 81.2%)

DOG	LEVEL	FATE	BACTERIOLOGY	REMARKS
87	1 cm. from pylorus	Died 96 hr.	Gm. + spore formers, rods, and streptococci, and Gm. - rods	Parasites extruding Generalized peritonitis
88	1 cm. from pylorus	Died 24 hr.		Perforation open Generalized peritonitis
89	3 cm. from pylorus	Died 24 hr.		Perforation open Generalized peritonitis
90	Midpancreas	Died 36 hr.		Perforation open Generalized peritonitis
91	Midpancreas	Died 48 hr.		Perforation open Generalized peritonitis
92	Midpancreas	Died 3 wk.		Perforation open Generalized peritonitis Peritonitis at 1 week Sealed by exudate Died of pneumonia
93	Midpancreas	Survived		
94	Tail of pancreas	Died 96 hr.	Gm. + rods, staphylococci, and streptococci, and Gm. - rods	Perforation open Generalized peritonitis
95	Tail of pancreas	Died 24 hr.	Gm. + anaerobes, rods, and spore formers. Gm. - rods	Perforation open Generalized peritonitis
96	Tail of pancreas	Survived		Signs of peritonitis early, but recovered
97	Tail of pancreas	Died 24 hr.		Perforation open Generalized peritonitis
98	Tail of pancreas	Died 72 hr.	Gm. + spore formers and rods. Gm. - rods	Perforation open Generalized peritonitis
99	Midpancreas	Survived		Transverse incision Laparotomy at one week revealed fat necrosis
100	Midpancreas	Died 24 hr.		Transverse incision, open—peritonitis
101	Midpancreas	Died 72 hr.	Mixed organisms	Transverse incision, open—peritonitis
102	Midpancreas	Died 72 hr.	Mixed organisms	Transverse incision, open—peritonitis

imals a longitudinal incision was made on the antimesenteric border at levels varying from one centimeter from the pylorus to the level of the tail of the pancreas. Ten of these animals expired. One of the survivors showed signs of peritonitis but recovered. In four dogs a transverse incision was used. Three of these animals died from peritonitis. The survivor was sacrificed in one week and showed marked fat necrosis throughout the peritoneal cavity.

VI. Perforation of the jejunum at distances varying from fifteen to ninety centimeters from the duodenojejunal angle was carried out in nine dogs. The mortality rate from peritonitis was 44.4 per cent (Table VI). There was no definite relationship between the level of perforation and the mortality rate.

In three dogs the Exalto-Mann-Williamson operation was performed in the hope of producing ulcers that might be experimentally

TABLE XI  
PERFORATION OF RECTUM OF DOG  
(FASTING ANIMALS)  
(MORTALITY 12.5%)

DOG	FATE	REMARKS
138	Survived	Perforated through anus. Sacrificed in 1 week. No peritonitis. No adhesions
139	Survived	Perforated through anus. Sacrificed in 5 days. No peritonitis. No adhesions
140	Survived	Perforated through anus. No peritonitis
141	Survived	Perforated through anus. No peritonitis
142	Survived	Perforated through anus. No peritonitis
143	Survived	Perforated through anus. No peritonitis
144	Survived	Perforated through anus. No peritonitis
145	Died 24 hr.	Perforated through anus. Severe generalized peritonitis. Mixed organisms

peritoneal cavity was verified in each instance by abdominal exploration. Only one animal succumbed, a mortality of 12.5 per cent. The others showed a small linear scar without the formation of adhesions.

#### DISCUSSION

The degree of infection which will develop following perforation of the gastrointestinal tract depends upon the number and virulence of the escaping organisms and upon the local and general resistance of the host.

Bacteriologic studies by various investigators<sup>3, 8</sup> have shown that the gastrointestinal tract is free from bacteria at the time of birth. The ingestion of organisms with the food, however, soon leads to the establishment of an abundant intestinal flora, and it has been estimated that a normal adult excretes daily in the feces nearly thirty trillion bacteria.<sup>8</sup> The food itself does not contain this large number of organisms, but there is bacterial proliferation within the alimentary canal.

Studies of the contents of the gastrointestinal tract a few hours after a meal<sup>3, 5</sup> have revealed the presence of a fairly large number of organisms in the stomach. There is a pronounced diminution in number in the duodenum, with a gradual increase to the region of the ileocecal valve where the number is the greatest. In the large intestine there is a marked decrease in the number of bacteria. The variety of organisms is great but the colon bacillus is the predominant type.

Gilbert and Dominici<sup>5</sup> determined the number of organisms in different parts of the alimentary canal of dogs two and a half and three hours after a meal of bread and meat. Their findings are summarized in a diagram which is reproduced in Fig. 3.

The acid gastric juice exerts a deleterious effect upon bacteria and gradually decreases the number of organisms in the stomach. In the duodenum there is a distinct decrease in the relative number of bacteria, probably due to the dilution of the chyme by the biliary

TABLE VIII

PERFORATION OF LOWER ILEUM OF DOG, 24 CM. PROXIMAL TO CECUM  
(FASTING ANIMALS)  
(MORTALITY 100%)

DOG	FATE	BACTERIOLOGY	AUTOPSY
115	Died 24 hr.	Gm. + rods, spore formers, and short chained streptococci. Gm. - rods	Perforation open Generalized peritonitis
116	Died 24 hr.	Gram positive rods	Perforation open Generalized peritonitis
117	Died 24 hr.	Gm. + rods, short chained streptococci, and rare Gm. negative rods	Perforation open Generalized peritonitis
118	Died 24 hr.	Gm. + anaerobes, rods, staphylococci, and streptococci, and Gm. - rods	Perforation open Generalized peritonitis
119	Died 48 hr.	Gm. + anaerobes, rods, many streptococci, few staphylococci, Gm. - rods	Perforation open Generalized peritonitis
120	Died 48 hr.	Gm. + diplococci, streptococci, and rods. Rare Gm. - rods	Perforation open Generalized peritonitis
121	Died 48 hr.	Gm. + rods, rare spore formers, and rare Gm. - rods	Perforation open Generalized peritonitis
122	Died 72 hr.	Gm. + anaerobes, diplococci, and rods. Few Gm. - rods	Perforation open Generalized peritonitis
123	Died 72 hr.	Gm. + anaerobes, diplococci, and rods	Perforation open Generalized peritonitis

In seven dogs in which the cecum was perforated, two died, a mortality of 28.5 per cent (Table IX). An identical mortality was found (28.5%) in a similar series of perforations of the descending colon (Table X).

TABLE IX

PERFORATION OF CECUM OF DOG  
(FASTING ANIMALS)  
(MORTALITY 28.5%)

DOG	FATE	AUTOPSY
124	Survived	Perforation healed without adhesions
125	Survived	Perforation healed without adhesions
126	Survived	Perforation healed without adhesions
127	Survived	Perforation healed without adhesions
128	Survived	Perforation healed without adhesions
129	Died 24 hr.	Perforation open. Generalized peritonitis. Gm. + rods and streptococci, and Gm. - rods
130	Died 36 hr.	Perforation open. Generalized peritonitis. Mixed organisms

TABLE X

PERFORATION OF DESCENDING COLON OF DOG  
(FASTING ANIMALS)  
(MORTALITY 28.5%)

DOG	FATE	AUTOPSY
131	Survived	Not sacrificed
132	Survived	Not sacrificed
133	Survived	Not sacrificed
134	Survived	Not sacrificed
135	Survived	Not sacrificed
136	Died 24 hr.	Perforation open. Generalized peritonitis. Gram positive rods and streptococci and gram negative rods
137	Died 72 hr.	Perforation open. Peritonitis. Mixed organisms

In eight animals the rectum was perforated by means of a scalpel introduced through the anus (Table XI). Perforation into the

TABLE XI  
PERFORATION OF RECTUM OF DOG  
(FASTING ANIMALS)  
(MORTALITY 12.5%)

DOG	FATE	REMARKS
138	Survived	Perforated through anus. No adhesions. Sacrificed in 1 week. No peritonitis.
139	Survived	Perforated through anus. No adhesions. Sacrificed in 5 days. No peritonitis.
140	Survived	Perforated through anus. No peritonitis.
141	Survived	Perforated through anus. No peritonitis.
142	Survived	Perforated through anus. No peritonitis.
143	Survived	Perforated through anus. No peritonitis.
144	Survived	Perforated through anus. No peritonitis.
145	Died 24 hr.	Perforated through anus. Severe generalized peritonitis. Mixed organisms.

peritoneal cavity was verified in each instance by abdominal exploration. Only one animal succumbed, a mortality of 12.5 per cent. The others showed a small linear scar without the formation of adhesions.

#### DISCUSSION

The degree of infection which will develop following perforation of the gastrointestinal tract depends upon the number and virulence of the escaping organisms and upon the local and general resistance of the host.

Bacteriologic studies by various investigators<sup>3, 8</sup> have shown that the gastrointestinal tract is free from bacteria at the time of birth. The ingestion of organisms with the food, however, soon leads to the establishment of an abundant intestinal flora, and it has been estimated that a normal adult excretes daily in the feces nearly thirty trillion bacteria.<sup>8</sup> The food itself does not contain this large number of organisms, but there is bacterial proliferation within the alimentary canal.

Studies of the contents of the gastrointestinal tract a few hours after a meal<sup>3, 5</sup> have revealed the presence of a fairly large number of organisms in the stomach. There is a pronounced diminution in number in the duodenum, with a gradual increase to the region of the ileocecal valve where the number is the greatest. In the large intestine there is a marked decrease in the number of bacteria. The variety of organisms is great but the colon bacillus is the predominant type.

Gilbert and Dominici<sup>5</sup> determined the number of organisms in different parts of the alimentary canal of dogs two and a half and three hours after a meal of bread and meat. Their findings are summarized in a diagram which is reproduced in Fig. 3.

The acid gastric juice exerts a deleterious effect upon bacteria and gradually decreases the number of organisms in the stomach. In the duodenum there is a distinct decrease in the relative number of bacteria, probably due to the dilution of the chyme by the biliary

and pancreatic fluids.<sup>5</sup> As the chyme passes downward, however, there is a multiplication of the bacteria which find more favorable conditions for growth as they escape the pronounced acidity of the upper portion of the canal.

After a period of starvation, the number of organisms is greatly diminished and the stomach and duodenum become relatively amicrobic.<sup>3</sup> Lower in the intestine, however, there remain a considerable number of bacteria even after a prolonged fast. Kendall<sup>8</sup> found a large number of colon bacilli in the large intestine of a man who had fasted for thirty days.

We found that openings in the normal stomach wall seal themselves soon after perforation and leakage occurs for only a very short time. When there is no food present, very little material escapes, and that which does reach the peritoneal cavity contains relatively few organisms. When the stomach contains food, however, enough material is likely to escape, even in a short time, to institute a severe infection of the peritoneal cavity. The mortality in such cases is

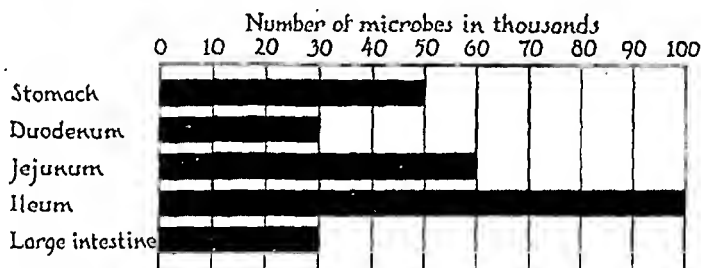


Fig. 3.—Relative number of bacteria in various parts of the alimentary canal of the dog, according to Gilbert and Dominici.

high, but if the infection is not overwhelming the animal may survive. Several dogs were able to withstand the escape of moderate amounts of milk or water (fluids which contain relatively few pathogenic bacteria) into the peritoneal cavity. Our results, however, differ from those of Himmelmann, who states that animals often survive even after the escape of large amounts of food from the stomach.

When sealing of the perforation is hindered, as for example by the injection of a substance which produces edema and delays closure, more material is permitted to escape and the mortality in fasted animals rises from 6.9 per cent to 40 per cent.

Openings into the intestine, on the other hand, seal themselves slowly, and early closure is only partially accomplished by a pouting of the mucosa into the defect. This difference between the stomach and the intestine might be explained by the difference in the arrangement of the muscular coats, the muscular tunic of the stomach being both heavier and more intricately arranged than that of the intestine. (Detailed descriptions of the muscular arrangement may be found in textbooks of anatomy.)

The high mortality (100 per cent) following perforations in the terminal ileum is not surprising, because, not only does this region have the most abundant flora of the entire intestinal tract, but the contents are fluid and considerable amounts readily escape when the wall is perforated. Jejunal perforations are less often fatal.

Since the duodenum in fasting animals contains few organisms, the 81.2 per cent mortality following duodenal perforations was a distinct surprise. The most likely explanation is that the duodenal juices which escape into the peritoneal cavity lower the local resistance sufficiently to enable the few organisms present to set up a fatal peritonitis. Blalock<sup>1</sup> has shown that bile and pancreatic juice are injurious to the peritoneum, producing fat necrosis and reddening of the peritoneal surfaces. The local injury probably favors the development of peritonitis. According to Blalock, gastric juice is less harmful than the duodenal juices and our results might be interpreted as confirming his findings.

Paas<sup>22</sup> has made the interesting observation that perforation of the duodenum in dogs induces a temporary reflex spasm of the pylorus which prevents the emptying of the stomach contents into the duodenum. He found that when he closed the perforation within four and a half hours after it had been established the dogs survived. When the perforation was not sutured and the dogs were fed a barium mixture, four of his five dogs died from peritonitis (80 per cent).

Defects in the colon, like those in the small intestine, close slowly, but due to the consistency of the contents of the normal large bowel there is less escape into the peritoneal cavity. Furthermore, the number of viable bacteria in this part of the intestinal tract is less than in most parts of the small intestine.

The mortality following rupture of the gastrointestinal tract as observed by the clinician is governed by the same factors that determine the mortality in experimental perforation. These may be briefly listed as follows:

#### I. The number and virulence of the escaping organisms

1. Size of the perforation
2. Length of time the perforation remains open
3. Number of organisms at the level of the perforation
  - a. Site of the perforation
  - b. Length of time after the ingestion of food
4. Amount and fluidity of material in the viscus at the time of perforation
5. Forces tending to carrying contents of the viscus out into the peritoneal cavity

#### II. Resistance of the host

1. General
2. Local—may be affected by duodenal juices

and pancreatic fluids.<sup>5</sup> As the chyme passes downward, however, there is a multiplication of the bacteria which find more favorable conditions for growth as they escape the pronounced acidity of the upper portion of the canal.

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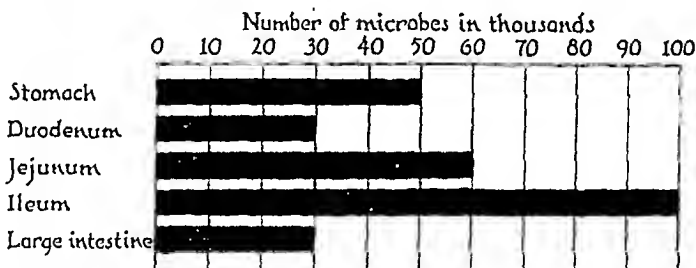


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ileum had succumbed to an ensuing peritonitis, though many of them had been operated upon at a comparatively early period and favorable prognoses had been given."

Further evidence has been supplied by cases of accidental perforation of the empty stomach during examination with the flexible gastroscope. Five such cases have been reported in the literature<sup>12</sup> and one occurred in our own clinic. All of these six cases recovered without ill effects. The case from our clinic showed pneumoperitoneum on x-ray examination but failed to develop any signs of peritonitis and recovered completely without operation.

The amount and fluidity of material in the viscus affect the mortality by influencing the ease with which material escapes through the perforation.

Traumatic rupture of the intestinal tract almost always results in great contamination of the peritoneal cavity, because the injuring force

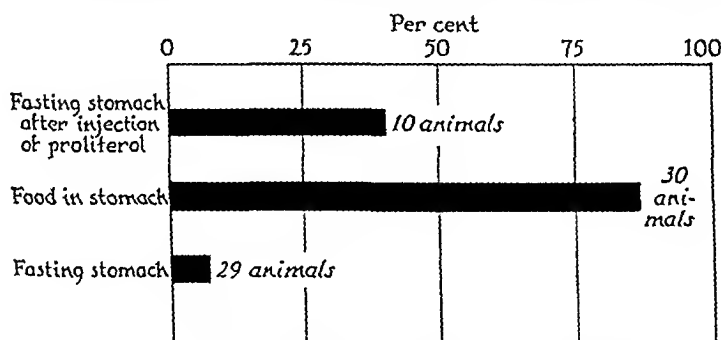


Fig. 5.—Mortality following perforations of the stomach.

carries intestinal contents out into the peritoneal cavity. A striking example of this is the compressed air rupture of the pelvic colon.<sup>10</sup> The outlook in such cases is distinctly unfavorable because of the widespread peritoneal contamination.

The other factors, the local and general resistance of the host, influence the mortality in clinical cases just as they do in the experimental animal.

These observations emphasize the importance of therapeutic measures directed at early closure of the perforation. Furthermore, in lesions involving the stomach or duodenum, evacuation of the contents of the viscus should be accomplished and maintained by continuous suction.<sup>13</sup> Even as late as the beginning of the World War (1914-1918) some well-recognized surgeons on both sides engaged in the conflict advocated conservative therapy for perforating gunshot wounds of the abdomen.<sup>4, 9</sup> Anyone who still doubts the validity of operation in cases of penetration



It is evident that a large perforation will not only allow the contents of the involved viscous to escape more readily but will also be less likely to seal itself spontaneously.

All surgeons are well aware of the fact that immediate closure of a perforating lesion of the gastrointestinal tract greatly reduces the mortality. Conditions are less favorable for spontaneous closure in clinical cases than in the normal experimental animal. The inflammatory reaction around an ulcer, for example, must definitely retard sealing of the opening. Some indication of this is given in the series of animals in which the injection of a sclerosing solution into the stomach wall preceded the perforation. Clinically, too, we know that perforated ulcers often remain open for long periods. The location of the lesion is also important in determining the time the perforation will remain open. Defects in the normal stomach close almost immediately, probably because of the intricate arrangement of the

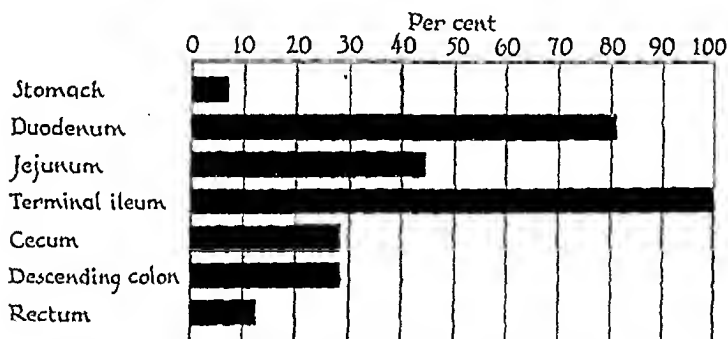


Fig. 4.—Mortality following perforation of the gastrointestinal tract in fasting animals.

muscular tunic. Intestinal perforations, however, gape widely and early but insecure closure is only partially accomplished by a pouting of the mucosa into the defect.

The number of organisms at the level of the perforation depends upon the site of the perforation and the length of time after ingestion of food. Although knowledge of the bacteriology of the intestinal tract is still limited, it is interesting that the mortality curve for our animals (Fig. 4) follows rather closely (except for the high mortality associated with duodenal perforations) the curve of Gilbert and Dominici (Fig. 3).

Clinical evidence supports experimental data. Cushing and Livingston after reviewing their cases of perforating gunshot wounds of the abdomen stated that "recovery had followed in those cases alone in which the perforations had been situated at no great distance from the pyloric end of the intestine, whereas all of the cases in our particular series in which the perforations had been far down in the

# PRIMARY CARCINOMAS OF THE STOMACH AND SIGMOID FLEXURE OCCURRING SIMULTANEOUSLY IN THE SAME INDIVIDUAL

JOHN DEJ. PEMBERTON, M.D., AND JOHN M. WAUGH, M.D.,  
ROCHESTER, MINN.

*(From the Mayo Clinic)*

**M**ULTIPLE primary carcinomas which affect the same individual have aroused the interest of the profession since the first reports of such lesions in 1869 by Billroth, although the frequency with which present-day pathologists report this finding is tending to make it almost commonplace. However, the finding clinically of two separate and distinct carcinomas appearing simultaneously in the sigmoid flexure and stomach is rare, and this, coupled with the fact that both lesions were amenable to surgical treatment, makes the report of the following case unique.

## REPORT OF CASE

A male physician, aged fifty-seven years, came to the Mayo Clinic, August 17, 1935, complaining of constipation which had been present for three months and attacks of intestinal obstruction. About three weeks prior to his admission, he had had his first severe episode of obstruction, which had been associated with nausea, distention, and cramps. The attack had been relieved in about four days by enemas and pitressin. A barium enema revealed an obstruction in the sigmoid flexure. After a barium meal had been given, the patient had another similar severe episode of obstruction and was rushed by plane to the clinic. He had lost 15 pounds (6.8 kg.) in two months. Examination at the clinic revealed that the acute intestinal obstruction had subsided; the abdomen was flat, soft, and not tender. There was a visible and palpable mass in the region of the sigmoid flexure. This mass was about  $4\frac{1}{2}$  inches by 2 inches (11.43 cm. by 5 cm.); it was firm, nodular, and freely movable. Except for a chronic "cigaret" cough, he had no other complaints.

His past history revealed that he had had osteomyelitis of the right mandible in 1934, and an appendectomy had been performed in 1900. Urinalysis and examinations of the blood did not reveal any abnormality. Roentgenoscopic examination of the colon with a barium enema revealed a carcinoma of the sigmoid flexure at the junction of the sigmoid flexure and the descending colon. Proctoscopic examination of the rectum and sigmoid flexure did not reveal any abnormality except hemorrhoids.

The clinical diagnosis was carcinoma of the proximal portion of the sigmoid flexure. Exploration of the tumor was undertaken by one of us (J. deJ. P.), August 22, 1935, using spinal anesthesia. Preliminary exploration of the upper part of the abdomen for metastasis disclosed a tumor about the size of the fist which involved the distal third of the stomach. This tumor was firm and had sharp nodular edges. It was believed to be another primary malignant tumor

Received for publication, January 12, 1937.

of the gastrointestinal canal by missiles from firearms should read the illuminating report of Enderlen and Sauerbruch<sup>4</sup> in which the superiority of the immediate operative attack is unequivocally shown.

#### SUMMARY

1. The factors influencing the mortality following perforation of the gastrointestinal tract have been enumerated.
2. Experimental perforations have been established at different levels in animals and the results tabulated.
3. The mortality following perforation of the empty stomach was 6.9 per cent, but when the stomach contained food the mortality rose to 86.7 per cent. Injection of a sclerosing solution into the stomach wall before perforation increased the mortality in fasting animals to 40 per cent.
4. In the small intestine the mortality was 81.2 per cent following duodenal perforation, 44.4 per cent following jejunal perforation, and 100 per cent following perforation of the terminal ileum.
5. The mortality following perforation of the large bowel was 23.1 per cent.

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# PRIMARY CARCINOMAS OF THE STOMACH AND SIGMOID FLEXURE OCCURRING SIMULTANEOUSLY IN THE SAME INDIVIDUAL

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which should be removed at a later date. There was no evidence of metastasis from either tumor. The carcinoma in the sigmoid flexure had perforated onto the lateral wall of the peritoneum but was definitely operable, so the portion of bowel about and including the tumor was brought outside as the first stage of the Mikulicz operation. The second stage of the operation, which was performed August 31, 1935, included removal of the growth with cautery. The pathologic report was adenocarcinoma, grade 2, of the sigmoid flexure without involvement of the lymph nodes. A clamp was applied to the colonic spur at the Mikulicz stoma.

At this time, clinical examination of the lesion in the stomach was undertaken. Roentgenoscopy examination with the barium meal showed a large ulcerating carcinoma of the pyloric end of the stomach with perforation; the lesion appeared to be operable locally. Aspiration of the gastric contents did not reveal any free hydrochloric acid. The value for the total acidity ranged from 10 to 16 according to the method of Töpfer.

Subtotal resection of the stomach was undertaken on September 19, 1935, by one of us (J. deJ. P.), using ethylene anesthesia. The approach was through an upper midline incision. The growth was freely movable in the pyloric end of the stomach and formed a mass which was the size of a doubled fist. There was no metastasis. A resection of the pyloric two-thirds of the stomach was done by turning in the end of the duodenum and making an anterior Polya type of anastomosis with an entero-anastomosis between the proximal and distal limbs of the jejunum. A small tumor about 1 cm. in diameter which was found in the upper part of the jejunum was removed. Microscopically it proved to be a neurofibroma. The lesion in the stomach was found to be an ulcerating adenocarcinoma, grade 2. There was no involvement of the lymph nodes.

The convalescence was very satisfactory, and after the application of clamps to the colonic spur, the opening in the colon at the site of the Mikulicz operation was closed, and when the patient was discharged, January 13, 1936, both wounds were well healed.

When he returned to the clinic, August 18, 1936, for reexamination, he said that he had been feeling very well and had been working daily. Careful physical examination, as well as roentgenologic examination of the thorax, colon, and stomach, failed to reveal the slightest evidence of recurrence or metastasis.

Although the patient was a physician, he insisted that he never had had the slightest symptom referable to his stomach or epigastrium. He always had been able to eat or drink with impunity. This is of interest because of the large size of the growth in the stomach, its ulceration and position at the outlet, all of which should have made the lesion prone to produce symptoms. It was very gratifying to all concerned that after a year no recurrence of either lesion was demonstrable by careful roentgenoscopy.

#### COMMENT

Warren and Gates, in an encyclopedic review of the literature in 1932, found 1,259 reported cases of multiple malignancy which they believed authentic, including their own cases. Practically all of these lesions were found at necropsy. These authors, as well as Hanlon, rightfully found Billroth's original criteria for the diagnosis of multiple primary malignancy too strict and substituted the following rules: (1) Each of the tumors must present a definite picture of malignancy; (2) each must be distinct; and (3) the probability of one's being a metastasis of the other must be excluded.

Hanlon, in reviewing 3,000 necropsies at the clinic, found 710 cases of malignancy, among which there were eighteen instances of multiple primary carcinomas. In these latter cases, the colon was involved nine times and the stomach three. In only two cases were the multiple growths recognized clinically. About half of the tumors were "silent" and did not give rise to any symptoms. Hurt and Broders, in an analysis of 2,124 cases in which microscopic examination revealed the presence of carcinoma, found that seventy-one of the patients previously had had carcinoma. They estimated that in 4 per cent of the cases in which a carcinoma is found, the patients have or will have later another independent carcinoma. In their series of 152 distinct lesions, the colon was affected in nine cases and the stomach in only one case. Hurt and Broders concluded that "multiple primary malignant neoplasms occur most commonly in the same organ or in organs of the same system. From the study of cases of multiple malignant neoplasms, it seems that the factors which cause the development of the tumors also express themselves in the grade of malignancy of the tumors." This latter fact is well borne out by the two lesions in the case reported, both of which were grade 2.

Warren and Gates, in their review of the literature prior to 1932, found the colon and stomach to be involved with simultaneous independent carcinomas in thirty of 1,259 cases of multiple primary carcinomas which they collected. In only three of these thirty cases was it definitely stated that the sigmoid flexure was affected.

Since this publication in 1932, there have been four more reported instances of multiple primary carcinomas in the colon and stomach; in none of these cases was the sigmoid flexure involved and in only one case did the carcinomas appear simultaneously. These four cases were reported by the following authors: Cecil Joll, in 1932, reported the resection, in 1930, of a lymphosarcoma of the stomach in a case in which he had performed a combined abdominoperineal resection in 1928 for carcinoma of the rectum. E. S. Judd and J. R. Phillips, in 1934, reported the resection of a carcinoma of the rectum six and a half years after the removal of a carcinomatous gastric ulcer. M. P. Bull, in 1932, reported the interesting finding of multiple primary carcinomas involving the colon and stomach of two brothers. In one case, the transverse colon was simultaneously involved with the stomach; in the other case, the growth appeared in the right half of the colon subsequent to resection of the stomach. All four tumors were successfully removed surgically.

These four, with our case, make a total of thirty-five reported instances of independent carcinomas which involved the colon and stomach. In only four of these cases was the sigmoid flexure involved.

The case herein cited is, so far as we are aware, the only recorded instance of successful surgical removal of simultaneous independent carcinomas of the stomach and sigmoid flexure.

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## ACUTE APPENDICITIS: A STUDY OF ONE THOUSAND CONSECUTIVE PATIENTS

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THIS report is based on the cases of acute appendicitis admitted to the Vanderbilt University Hospital during a period of approximately 10 years. The majority of the patients have come from rural districts, many of them from distances of 100 miles or more. The series includes private patients, but these compose only about 15 per cent of the entire group. The instances in which the appendix was removed during the course of an operation for some other condition are not included, nor are those cases in which the diagnosis was not substantiated by either operation or autopsy.

The study was undertaken to determine the mortality of the entire group, the mortality of the group in which the appendix was ruptured, and, if possible, to determine the factors which influenced the mortality in the latter group.

All patients are sent from the admitting office to the wards and never directly to the operating room. Those patients who have peritonitis are seen by the resident surgeon and by a senior staff surgeon. If the patient is dehydrated, regardless of the stage of the inflammatory process, operation is deferred for a time sufficient to administer fluids. Should further delay be thought advisable, the patient is given nothing by mouth; fluids are administered subcutaneously; and morphine is given at frequent intervals.

Postoperatively these same measures are usually employed. Frequent small blood transfusions are given in many cases in which the appendix is ruptured, and are believed to be of definite value. Vomiting is combated by the use of duodenal suction siphonage.

Most of the operations are performed by the resident surgeon, usually in the fourth or fifth year of his surgical training, and a comparison of each surgeon's mortality rate shows very little variation. McBurney's incision has been used in relatively few instances, the Battle-Kammerer incision being used in most of the operations. The appendix has been found in most instances to be easily accessible with this approach. Most of the operations have been performed under general anesthesia, local anesthesia being used only when nitrous oxide and ether were thought to be definitely contraindicated. No definite routine is observed regard-



ing delay in operation on patients with peritonitis. This point will be considered later. Where removal of the appendix in the presence of peritonitis necessitates a long anesthetic or much manipulation, drainage without an attempt to remove the appendix has generally been practiced.

The series is divided into two main groups; viz., the patients in whom the appendix was not ruptured, and those in whom the appendix was ruptured. The latter group is subdivided as follows:

*Appendiceal Abscess.*—Those patients in whom the inflammatory process is well walled off around or near the appendix.

*Localized Peritonitis.*—The cases in which the inflammatory process is still confined to the region of the appendix and has not been walled off to form an abscess.

*Spreading or Generalized Peritonitis.*—The cases in which the inflammatory process has spread to involve a large portion of the peritoneal cavity without evidence of localization.

TABLE I  
MORTALITY RATES IN FIVE-YEAR AGE GROUPS

AGE LIMITS	NUMBER OF CASES ACUTE APPENDICITIS	RUPTURED APPENDICITIS	TOTAL NUMBER OF CASES	NUMBER OF DEATHS (TOTAL)	MORTALITY (TOTAL) PER CENT
0-5	4	9	13	3	23.0
6-10	31	36	67	6	9.0
11-15	100	59	159	10	6.3
16-20	182	54	236	8	3.4
21-25	159	33	192	4	2.1
26-30	88	28	116	6	5.2
31-35	40	23	63	4	6.3
36-40	33	16	49	2	4.8
41-45	17	20	37	6	16.2
46-50	14	14	28	2	7.1
51-55	7	9	16	2	12.5
56-60	5	5	10	1	10.0
61-65	2	5	7	2	28.5
66-70	0	4	4	1	25.0
71-75	0	1	1	0	0

In the 1,000 cases, there were 57 deaths, but 6 of the patients who died were not operated upon, for reasons which will be given in detail later. The mortality rate in the 994 cases operated upon was 5.1 per cent.

*Color.*—There were 876 white and 124 colored patients. In 252 of the white patients, or 28.8 per cent, the appendix was ruptured, and there were 45 deaths, the mortality rate being 5.1 per cent. In the group of colored patients, 64, or 51.6 per cent, had ruptured appendices, and the mortality rate was 9.7 per cent, there being 12 deaths.

*Sex.*—The incidence of appendicitis was predominant in males. Of the 587 male patients, 215, or 36.9 per cent, had ruptured appendices; 38 of these patients died, a mortality rate of 6.5 per cent. In the 413 female patients, the appendix was ruptured in 99, or 23.9 per cent, and there were 19 deaths, a mortality rate of 4.6 per cent.

*Age.*—In Table I, all cases are divided into 5-year age groups. The mortality rate is seen to be considerably higher in patients below the age of 10 years and above the age of 50 years than in the groups between these limits and is lowest in the period between the ages of 15 years and 25 years. The incidence of the disease is the inverse of this, being highest in the 15-year to 25-year group and lowest in the extremes of life. It is also interesting to note that the proportion of ruptured to unruptured appendicitis is higher in the very young and very old.

*Mortality Rate for Each Year.*—This is shown in Table II. There were no deaths in 1925 or in 1928, although in one-third of the cases in

TABLE II  
MORTALITY RATE FOR EACH YEAR

YEAR	TOTAL NUMBER CASES	NUMBER OF DEATHS	MORTALITY PER CENT
1925	15	0	0
1926	42	3	7.1
1927	38	.2	5.2
1928	66	0	0
1929	73	3	4.1
1930	87	5 (1 acute)	5.7
1931	138	7	5.1
1932	155	11	7.1
1933	149	6	4.0
1934	113	14	12.4
1935	124	7	5.6

1925 and in one-fourth of the cases in 1928, the appendix was ruptured. In 1934, there was a relatively large number of patients who were moribund at the time of admission. With the exception of the high mortality during this year, there is no definite trend toward a higher or a lower mortality in this series over the period of ten years. In Table III, the incidence of ruptured appendicitis is given for each year. It is interesting to note that there is an almost unbroken decrease in the ratio

TABLE III  
PERCENTAGE RUPTURED APPENDICES AT TIME OF OPERATION  
RATIO RUPTURED TO TOTAL NUMBER OF CASES DURING EACH YEAR

YEAR	NUMBER PATIENTS WITH UN- RUPTURED APPENDICES	NUMBER OF PATIENTS WITH RUPTURED APPENDICES	TOTAL	CASES RUPTURED AT OPERATION PER CENT
1925	10	5	15	33.3
1926	23	19	42	45.0
1927	24	14	38	36.8
1928	51	15	66	22.7
1929	56	17	73	23.3
1930	69	18	87	20.6
1931	99	39	138	28.2
1932	116	39	155	25.1
1933	98	51	149	34.2
1934	65	48	113	42.5
1935	74	50	124	40.3

of ruptured cases to the total number until the time of the recent economic depression, the incidence being 45 per cent in 1926 and 20.6 per cent in 1930. The ratio then became greater in each succeeding year until in 1934 it was 42.5 per cent, dropping back to 40.3 per cent in 1935.

*Duration of Symptoms.*—In Table IV, all cases operated upon are grouped according to the duration of the patients' symptoms, and the

TABLE IV  
DURATION OF SYMPTOMS AND MORTALITY RATE

DURATION OF SYMPTOMS AT TIME OF OPERATION	NUMBER OF CASES	NUMBER OF DEATHS	MORTALITY RATE PER CENT
0 to 24 hours	342	4	1.2
24 to 48 hours	247	11	4.5
48 to 72 hours	111	12	10.9
4th day	57	6	10.5
5th day	39	4	10.2
6th day	33	4	12.1
7th day	37	4	10.7
8th to 14th day	68	5	7.3
Over 14 days	60	1	1.7

mortality rate is shown for each group. As would be expected, the mortality is lowest in the patients operated upon during the first twenty-four hours. It is highest in the group operated upon during the sixth day, the mortality varying little in the five groups between the third and seventh days, inclusive. These groups include most of the patients with generalized peritonitis and all of the patients who were moribund at the time of admission.

There were 686 patients in whom the appendix was not ruptured, and 314 in whom the appendix was ruptured. Thus, 31.4 per cent of the total number of patients had ruptured appendices at the time of admission.

#### UNRUPTURED APPENDICES

In the group in which the appendix was not ruptured, there was only one death, a colored female of twenty-five years of age, who died three days after operation. Autopsy was limited to exploration of the wound at the undertaking parlor. There was no evidence of hemorrhage, infection, or intestinal obstruction. Clinically, the death was thought to be due to massive pulmonary collapse. This is a mortality rate of 0.145 per cent in this group.

The following surgical pathologic diagnoses were made:

Acute appendicitis	494 cases
Subacute appendicitis	84 cases
Chronic obliterating appendicitis	39 cases
No microscopic lesion	69 cases

Of the 69 appendices in which there was no gross or microscopic evidence of inflammation, 13 were removed as "interval appendec-

tomies" because of the history of repeated attacks of right lower quadrant pain. Sixteen had abdominal pain at the time of admission, but operation was delayed from twelve hours to four days after admission. These patients were carefully studied and operation advised because of previous attacks. In the remaining 40 patients, the operation was performed immediately, but in 9 of these, other conditions, such as urinary infection, were recognized before operation. In 31 cases out of the 1,000, there was no history of previous attacks. Operation was performed immediately and a normal appendix removed, and nothing else was found to account for the patient's symptoms.

#### RUPTURED APPENDICES

The 314 patients with ruptured appendices were the ones most carefully studied. There were 56 deaths in this group, but 6 patients not operated upon are excluded, leaving 50 deaths, a mortality rate of 16.3 per cent for all cases of ruptured appendicitis in which operation was performed.

In Table V, the entire series is divided into the four groups as previously outlined, and the mortality rate for each group is shown.

TABLE V

CLASSIFICATION ACCORDING TO THE STAGE OF THE DISEASE—MORTALITY RATES

	NUMBER OF CASES	NUMBER OF DEATHS	MORTALITY PER CENT
Acute appendicitis	686	1	0.145
Appendiceal abscess	118	5	4.2
Localized peritonitis	87	7	8.1
Spreading or generalized peritonitis	103	38	36.9

*Appendiceal Abscess.*—There were 118 patients with appendiceal abscess, 5 of whom died, mortality rate of 4.2 per cent. In this group, operation was performed immediately in 63 cases and was delayed in 55. All of the 5 deaths are included in the group of 55 in which operation was delayed. The appendix was removed at the time of the first operation in 79 cases; and in 39 cases, the abscess was drained without an attempt to remove the appendix. Four of the deaths were in the latter group; 1 dying of lobar pneumonia, and another dying of a pulmonary embolus, both having had satisfactory courses before onset of the complication. The 3 remaining patients died of generalized peritonitis.

*Localized Peritonitis.*—There were 87 cases of localized peritonitis with 7 deaths, a mortality rate of 8.1 per cent. Operation was performed immediately upon all of these patients, and the appendix removed in all cases except 1, the patient making an uneventful recovery in this one

instance. Five of the deaths were due to generalized peritonitis, the other 2 dying of extensive bronchopneumonia, the diagnosis being verified by portable roentgenograms.

*Spreading or Generalized Peritonitis.*—There were 103 patients in this group with 38 deaths, a mortality rate of 36.9 per cent. Operation was deferred in 25 cases, and 8 of these patients died, the mortality rate for this "deferred group" being 32 per cent. Seventy-eight patients were operated upon immediately, 30 of them dying, the mortality rate being 38.5 per cent. Of the 103 cases, the appendix was removed in 84, drainage alone being instituted in 19. There were 13 deaths in the small group in which the appendix was not removed. This is accounted for, in part, by the fact that out of 7 patients who were moribund or nearly so at the time of operation, the appendix was not removed in 5 cases, drains being inserted in the right iliac fossa under local anesthesia and the operation requiring only a few minutes' time.

Of the 258 cases of ruptured appendicitis which recovered, 132, or 51.2 per cent, had purgatives before admission. In the group of 50 deaths, 68 per cent had purgatives.

#### ANALYSIS OF DEATHS

At the time of operation, 38 out of the 50 of those who died had an unmistakable generalized peritonitis. Seven of these patients, as was noted previously, were moribund or nearly so. The anesthetist's records show that 6 of the patients who died had operation under novocaine anesthesia alone, and in 5 others, novocaine was supplemented by nitrous oxide. Six had nitrous oxide alone, and 33 had gas induction and ether anesthesia.

In 22 cases, the operation was completed in less than thirty minutes, the seven patients who were nearly moribund being included in this group. In the remaining 28 cases operation required from thirty to one hundred minutes, with an average of fifty-five minutes. This includes the entire time that the patient was on the table, the anesthetic being discontinued as soon as the peritoneum was closed.

The reasons for not operating on the 6 patients who were excluded are as follows:

Two of the patients were moribund on admission, both expiring about seven hours after they were admitted. One of them was a man sixty-five years old. Two others lived four and one-half and six days after admission. One had been sick seven days, the other three days, and both had generalized peritonitis. They showed signs of improvement with conservative treatment, but both became suddenly worse a few hours before death, quickly became moribund, and both died with generalized peritonitis.

The fifth patient was a twelve-year-old white girl who had been sick six days before admission, having had fever, chills, but no abdominal

pain or other symptoms suggesting appendicitis. On admission the abdomen was soft, and there was no evidence of localized intraperitoneal infection. She continued to have fever, and eight days after admission began again to have frequent chills. Careful study failed to reveal any cause for her fever. Twenty-four hours before death, which occurred on the sixteenth day, the abdomen became distended, and she developed unmistakable evidence of generalized peritonitis. Autopsy revealed a gangrenous perforated appendix, a rather early generalized peritonitis, septic thrombosis of the portal veins, and multiple liver abscesses.

The sixth patient was a four-year-old boy who had hydrocephalus. Two craniotomies were performed, an ependymablastoma obstructing the iter being partially removed at the second operation. Following this, he remained comatose, and his condition grew gradually worse with high daily temperature elevations and, after several days, with marked abdominal distention and signs of general peritonitis without any evidence of localization. At autopsy a gangrenous appendix and generalized peritonitis were found.

Autopsy was obtained in 37 cases and the following conditions were found:

Generalized peritonitis .....	35 cases
Bronchopneumonia .....	17 cases
Volvulus of ileum.....	4 cases
Subdiaphragmatic abscess .....	4 cases
Pylephlebitis and liver abscess.....	3 cases
Streptococcus septicemia .....	4 cases
Fecal fistula .....	1 case

In the 13 cases in which autopsy was not obtained, 11 patients had unmistakable evidence of generalized peritonitis before death. In one of the other cases, the patient had extensive lobar pneumonia and died on the tenth postoperative day. The other patient died on the eighth day, probably of a pulmonary embolus.

The 6 patients who were not operated upon were all found at autopsy to have generalized peritonitis. The single death in the series of cases in which the appendix was not ruptured was due to massive pulmonary collapse.

The causes of death were:

Generalized peritonitis .....	52 patients
Bronchopneumonia .....	2 patients
Lobar pneumonia .....	1 patient
Pulmonary embolus .....	1 patient
Massive pulmonary collapse .....	1 patient

#### DISCUSSION

A brief comparison of mortality rates in appendicitis recently reported by several other university hospitals is shown in Table VI.

The average of these figures for each group is given and a careful study shows that the mortality rates of each clinic vary little and are near the average figures for the entire group. There is basically little difference in the methods of treatment employed in these institutions. Pattison,<sup>1</sup> of the University of Iowa, found the mortality rate to be higher in the cases in which a right rectus incision was made than in those in which the McBurney incision was used, but he stated that this is suggestive and not conclusive evidence of the relative value of the two incisions. In 1934, Reid<sup>2</sup> reported 409 cases of acute appendicitis operated upon at Cincinnati General Hospital between the years 1915 and 1922, the right rectus incision being used routinely and the mortality rate being 9.8 per cent. In 1922, the McBurney incision was adopted and has been used exclusively from 1922 to 1934 in 1,626

TABLE VI  
COMPARISON OF MORTALITY STATISTICS IN UNIVERSITY HOSPITALS

	*UNIVERSITY OF MINNESOTA (SPERLING, L. <sup>6</sup> ) 1932-1934		UNIVERSITY OF MICHIGAN (COLLER AND POTTER) 1931-1933		UNIVERSITY OF IOWA (PATTISON) 1919-1934		YANDERBILT UNIVERSITY 1925-1935		AVERAGE MORTALITY
	NO. OF CASES	MORTALITY	NO. OF CASES	MORTALITY	NO. OF CASES	MORTALITY	NO. OF CASES	MORTALITY	
Simple acute appendicitis	110	0.99%	213	0.46%	814	0.37%	686	0.15%	0.49%
Appendiceal abscess	59	6.7%	35	5.7%	268	8.6%	118	4.2%	6.3%
Local peritonitis	21	9.5%	88	12.5%	48	4.2%	87	8.1%	7.7%
General peritonitis	46	43.4%			81	43.2%	103	36.9%	41.2%
Total	236	7.5%	336	4.1%	1211	5.2%	994	5.1%	5.5%

\*Since this paper was sent to the publishers, a more complete group of cases from the University of Minnesota by Sperling, L., and Myrick, J. C., has appeared in SURGERY 1: 255, 1937.

patients with acute appendicitis. The mortality rate for this period was 5.2 per cent. It seems possible that other changes in operative technique, as well as in the care of the patient preoperatively and postoperatively, may have contributed largely to this reduction in mortality rate. Keyes,<sup>3</sup> in 1934, reported 1,859 cases of appendicitis in the Barnes and St. Louis Children's Hospital with a mortality rate of 3.33 per cent; the right rectus incision had been used more frequently in that clinic. In our series of cases, the mortality rate for those operated upon is 5.1 per cent; the McBurney incision has been used infrequently except where drainage of an appendiceal abscess is instituted. The technical difficulties encountered in using the Battle-Kammerer incision are not great if the incision is not very long, if it is placed near the lateral border of the rectus muscle, and if one exercises the proper care in packing off the surrounding loops of intestine before removing the

appendix. If local anesthesia is used, the appendix can be removed with greater ease through a McBurney incision. There is actually so little difference between these two incisions that the advantages of each are probably overemphasized, and the improvements in the care of the patient, the importance of fluids and blood transfusions, and the wider choice of anesthetics are the factors which have lowered the mortality rate in the most recent series.

Coller and Potter<sup>4</sup> give an excellent discussion of the so-called "delayed" treatment of patients with ruptured appendicitis. They advocate delay of operation until the inflammatory process has become well walled off. In general, we feel that delay in operation is justified when there is no doubt that the appendix is ruptured and that the peritonitis is not spreading or that the patient's general condition may be greatly improved by delay. If the patient is markedly dehydrated, every attempt should be made to correct this before subjecting the patient to operation. The fact that the appendix is not ruptured in occasional cases in which a preoperative diagnosis of early ruptured appendicitis with localized peritonitis is made, justifies immediate operation on all of these patients.

There is complete agreement as to the value of immediate operation in all cases of unruptured appendicitis, but a wide difference of opinion exists as regards the proper treatment of patients with early generalized peritonitis who have been sick from three to five days. Many surgeons advocate immediate removal of the appendix with drainage, and as many more counsel delay of operation until an abscess forms, usually from ten to fourteen days after onset. We believe that each of these patients must be considered individually and if delay of operation is decided upon, then fluids subcutaneously and morphia in sufficient amounts should be given, but we always reserve the right of intervening if the patient does not seem to respond to conservative measures. We have not infrequently seen patients who had had generalized peritonitis for three or four days show improvement after complete rest and fluids for several days, and then on the sixth, seventh, or eighth day of peritonitis again have increased fever, rapid pulse, and vomiting. With drainage at this point, many of these patients show immediate improvement.

Drainage of the right iliac fossa and of the pelvis when the appendix is ruptured and free pus is present is deemed the wisest procedure in spite of the possibility of fecal fistula or intestinal obstruction later. These complications have been infrequent in this clinic. In an occasional patient with ruptured appendicitis the wound has been closed without drainage.

The persistent catharsis by the patient and family, and, more important, the late hospitalization of patients with appendicitis are still the factors that more than any others should be corrected. The results of



lay instruction are shown in Philadelphia, which has one of the lowest death rates of any city in the country and which has employed the best system of education of the laity.<sup>5</sup>

#### SUMMARY

1. A study of 1,000 consecutive patients in whom a diagnosis of acute appendicitis was made is presented. These patients were admitted to the Vanderbilt University Hospital between the years 1925 and 1935, inclusive.

2. The mortality rate for the entire group is 5.1 per cent, 6 patients who were not operated upon being excluded.

3. Of the 686 cases of unruptured acute appendicitis, there was 1 death, a mortality rate of 0.145 per cent.

4. Of the 308 cases of ruptured appendicitis in which operation was performed, there were 50 deaths, a mortality rate of 16.3 per cent.

5. The mortality rate and incidence of ruptured appendicitis are highest at the two extremes of life.

6. In approximately 1 case in every 3, the appendix was ruptured at the time of admission.

7. In more than half of the cases of ruptured appendicitis, the patients had received catharsis before admission.

8. Our own results agree closely with those recently reported by similar institutions.

9. The importance of considering each case individually and reserving the right to intervene in those cases in which delay is at first decided upon, is emphasized.

10. Instruction of the laity in the symptoms of acute appendicitis and in the value of early operation in these cases offers the best chance for reduction of the present mortality rate.

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## FUNDAMENTAL PRINCIPLES IN THE TREATMENT OF DIABETIC GANGRENE.

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**P**ROLONGATION of the life of the diabetic through the use of insulin has created an alarming increase in the occurrence of arteriosclerotic disease. Aside from the visceral manifestations of arteriosclerosis, such as coronary artery narrowing or thrombosis, the peripheral, arterial disturbances now seen so frequently in diabetic patients are worthy of serious consideration and study.

To avoid confusion, it is advisable to clarify the terminology of arteriosclerosis of the peripheral vessels, keeping in mind the underlying pathologic changes involved. In general, it may be stated that from the clinical standpoint the term arteriosclerosis has replaced the less commonly used atherosclerosis and endarteritis. When the arteriosclerotic process is combined with an obliteration of the arterial lumen either by narrowing or by thrombosis, it is qualified by adding the adjective *obliterans*. In other words, one may speak of arteriosclerosis of the peripheral arteries minus interference with blood flow. When, however, evidence of obstructed flow is also present, the condition should rather be described as one of arteriosclerosis *obliterans*, which is the preferred modern designation. In this connection it is important to note that extensive calcification of arteriosclerotic arteries may be visible on roentgen examination with, however, no evidence of impaired circulation resulting therefrom. This condition is properly described as arteriosclerosis with calcified arteries. When, however, there are also clinical signs or symptoms suggestive of impairment of the arterial onflow, the correct terminology is arteriosclerosis *obliterans* with calcification. If diabetes mellitus is also present, the proper designation is diabetic arteriosclerosis *obliterans*. With the appearance of gangrene, one speaks of either arteriosclerotic gangrene or diabetic arteriosclerotic gangrene. Since, however, almost every case of gangrene of the extremities in a diabetic is primarily of arteriosclerotic origin, it is simpler to employ the widely used designation diabetic gangrene in everyday parlance.

Another advantage in the use of the term arteriosclerosis *obliterans* is the clear distinction from the other important obliterating disease of the peripheral vessels, thromboangiitis *obliterans*.

lay instruction are shown in Philadelphia, which has one of the lowest death rates of any city in the country and which has employed the best system of education of the laity.<sup>5</sup>

#### SUMMARY

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5. Bower, J. O.: Appendicitis in Philadelphia, *J. A. M. A.* 102: 813, 1934.
6. The University of Minnesota Hospital Bulletin, Vol. 6, No. 8, Nov. 15, 1934.

be remembered, however, that only too often, even with the best of care, a diabetic arteriosclerotic limb must be sacrificed for an apparently insignificant lesion.

#### REST IN BED

At the first sign of impending gangrene, complete rest is imperative, not only because of the removal of local trauma but because of the necessity of maintenance of the limb in the horizontal position. If the extremity is held in the dependent position for even a short period of time, edema of the foot, and particularly of the involved area, soon appears. This causes greater pain and extension of the gangrenous process. Elevation of the foot is harmful since it causes further depletion of blood by the force of gravity. Hence, the horizontal position is preferable at all times. The natural physiologic advantages of complete rest are not to be neglected in the treatment of diabetic gangrene.

If conservative treatment eventually proves successful, the patient must remain in bed until complete healing has been achieved. This may prove impractical from the economic standpoint but is certainly imperative from the therapeutic standpoint.

#### SMOKING

The vasoconstricting action of smoking has been thoroughly demonstrated clinically and experimentally. For this reason it is advisable to prohibit completely the use of tobacco in all forms of peripheral arterial disease. Fortunately, this is not so great a problem in diabetic gangrene as it is in thromboangiitis obliterans. In the latter group, excessive cigarette smoking is the rule, while in the former, smoking, if indulged in at all, is usually extremely light.

#### LOCAL TREATMENT OF GANGRENE

The object of the local treatment of gangrene in the diabetic is to prevent, as far as possible, the development of secondary infection in the gangrenous area with its ultimate extension into the adjacent tissues. Gangrene, per se, is not as serious as the accompanying infection in diabetic subjects. Because of the menace of infection in diabetic gangrene, it is of the utmost importance that every precaution and care be taken in dressing and handling the involved parts. The crude practice of exposing a gangrenous foot under a cradle, with no dressing whatsoever, inviting contamination from flies, dirt, bedding and what not, is to be heartily condemned. In no other surgical condition is such treatment tolerated. Why, then, in a diabetic, whose susceptibility to infection is notorious?

In the incipient cases of interdigital gangrene and infection, daily gentle irrigation with warm boric acid solution is beneficial. This may be followed by the local application of a mild antiseptic, such as mercurochrome, and a protective covering of sterile gauze. If the infec-

## CLASSIFICATION

The onset of gangrene in the arteriosclerotic extremity may be precipitated by the gradual narrowing of the arterial channels or by sudden occlusion due to thrombosis. In the former group, the narrowing has usually progressed slowly enough over a long period of time to allow for the spontaneous formation of collateral circulation, sparse though it is in arteriosclerosis; whereas in the sudden occlusive type, there is hardly any time for the establishment of collateral circulation. (Group II.)

Recognizing the distinction between these two groups of arteriosclerotic gangrene, the fundamental principles involved in the treatment will be more readily understood. Cases falling into Group I are, in general, more amenable to conservative therapy and ultimate preservation of the limb because, as mentioned previously, there has been some attempt at the establishment of collateral circulation. Naturally, this is not quite as extensive or prolific as in the younger cases of thromboangiitis obliterans. The marked difference in formation of collateral circulation between the two conditions is well illustrated by arteriography.

## DEVELOPMENT OF GANGRENE

It will be found that the most frequent point of origin of diabetic gangrene in Group I is a fissure in an interdigital space. This fissure is almost always caused by an infection of epidermophyton, which is so prevalent today. For this reason, the hygiene and prophylaxis of the diabetic foot must include serious consideration of ringworm infection of the interdigital spaces. Absolute cleanliness of the feet with the daily application of a mild antiseptic such as mercurchrome, metaphen, or weak iodine is imperative. The danger lies not so much in the ringworm itself as in the introduction of secondary, pyogenic invaders into the fissures and open lesions caused by the primary organisms. As soon as the secondary infection is established, the mischief is done. Local edema and infection soon cause small areas of superficial gangrene in the interdigital spaces. The pressure of the edema on the poorly nourished tissues causes further extension of the gangrene, usually toward the base of the adjacent toes. Thus the existing diminished blood supply to these digits is shut off completely and within a short time discoloration and gangrene are observed. This is usually excruciatingly painful, although in some rare instances, in hyposensitive individuals, discomfort may be slight. If the collateral circulation in the extremity is maintained, the gangrenous process may be confined to one or more toes—if not, further extension to the dorsum of the foot will ensue.

The proper management of diabetic gangrene in this early stage is of the greatest importance if the extremity is to be conserved. It must

A continuous wet dressing may be of help, or in some cases a daily foot bath of soap and water, with, of course, sterile precautions. In some instances careful dissection along the line of demarcation may be necessary. The choice of procedure will vary with each case and the judgment of the surgeon.

After the gangrenous tissues have been removed, it will usually be found that the proximal ulcer is partially epithelized. This can be encouraged to proceed either by a wet dressing of boric acid solution or by a bland ointment dressing such as boric acid.

Another common point of origin of gangrene is a small fissure on the heel. Prevention of this condition is usually simple if the possibility of its development in all cases of deficient circulation is kept in



Fig. 2.—Same case as shown in Fig. 1, healed except for residual ulcer of stump of left big toe.

mind. Daily inunction of the feet with either olive oil or lanolin should be a routine procedure by the patient, and its importance should be constantly stressed. Special attention to the heels is desirable.

Gangrene of the heel may also develop from constant pressure on the bedding while the patient is being treated for some other condition. I have found that a voluminous dressing of soft absorbent cotton over the heels is superior to the customary "doughnut" or cotton ring in avoiding this undesirable complication.

Once established, gangrene of the heel is difficult to control. However, with meticulous care, very satisfactory results can often be obtained. The avoidance of secondary infection is particularly impor-

tion has become frankly purulent, the irrigation should be followed by a small wet dressing of boric acid solution, which should be kept wet. As the purulent secretion decreases in amount and the tissues appear relatively clean, the wet dressing may be discontinued and a dry dressing or boric acid ointment may be applied.

The technique of the dressing is important. The parts should be handled only with either sterile gloves or with forceps. A real surgical respect for the gangrenous tissues is imperative in the treatment of diabetic gangrene.

Dusting powders are not recommended because of their tendency to cover up and conceal pus, thus often causing extension of the infection, even if trivial, into the deeper tissues.

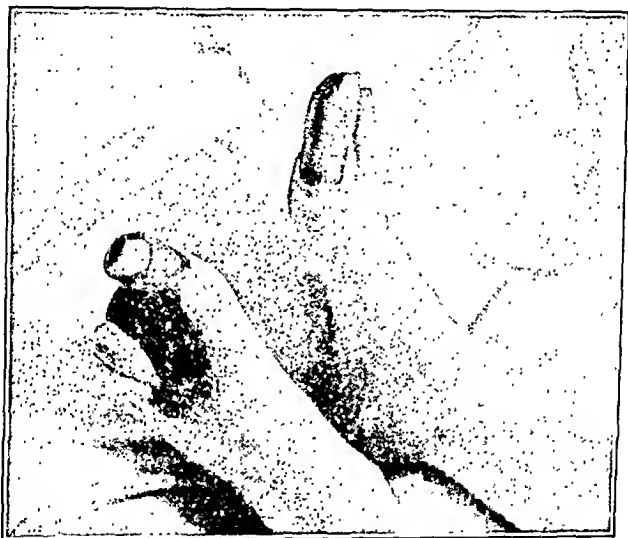


Fig. 1.—Diabetic gangrene. Spontaneous amputation of toes. Gangrene of right big toe produced by burn of lamp and cradle.

If one is fortunate enough to secure a definite localization of the gangrenous process with the establishment of a line of demarcation, one should not be too impatient and attempt a quick removal of the dead tissue. I have seen a number of such attempts end in disaster. This is particularly true in the case of individual toes. In one instance, seen recently, excellent demarcation of a single toe had been established, but the attending physician attempted to hasten matters by forcibly twisting off the black toe with an artery clamp. The next day the patient complained of pain and swelling in the adjacent part of the foot and within forty-eight hours there was definite evidence of infection along the flexor tendon. In spite of radical incision and drainage, amputation of the leg had to be done. It is preferable to allow sufficient time for spontaneous separation of the dead parts.

of cases of diabetic gangrene. The importance of prevention in this disease has not been sufficiently stressed.

In a case of established gangrene, efforts to aid in the development of additional collateral are necessarily handicapped, in contrast to the brilliant results obtainable in thromboangiitis obliterans. In the latter group, one deals with younger individuals with a remarkable tendency to the spontaneous development of collateral circulation. In the arteriosclerotic, the age is more advanced; spontaneous collateral is sparse and the reaction of stimulating agencies is weak. In addition, the older arteriosclerotic usually has an associated cardiac or renal impairment, or both, which adds more therapeutic difficulties. For these reasons, it is imperative that in the treatment of diabetic gangrene one is constrained to limit his enthusiasm to simple and safe procedures only, avoiding the spectacular, dangerous and impractical methods of treatment advocated only too often.

#### HEAT

In dealing with gangrene one must not lose sight of the fact that the local condition is usually only a small part of the entire extremity. Gangrene of one toe may be the result of a clot located in the external iliac artery. It must also be remembered that while one or more toes may be dying and cold, the remainder of the extremity is very much alive and capable of retaining and giving off a considerable amount of heat. Preservation of the natural heat of the entire extremity is a simple procedure. It can readily be attained by wrapping the limb in toto from groin to toes in a soft, warmth-retaining covering such as cotton or lamb's wool.

The use of external heat in diabetic gangrene, such as is obtained from an incandescent lamp or other source, is objectionable from two very important angles. In the first place, the danger of burns from accidental contact with the lamp or other source of heat is notorious. Because of the frequent occurrence of these disastrous burns, the use of the cradle and lamp is condemned. The second objection to external heat is the inability of the superficial tissues of the heated extremity to respond properly to the raised temperature applied. Increased heat requires a greater blood flow and an increased local metabolism of the superficial tissues. Neither of these is possible in these blood-starved extremities, resulting in considerable danger in the form of burns or of spreading gangrene, not to speak of the excellent incubation provided for saprophytic organisms lying dormant in the gangrenous tissues.

#### INTRAVENOUS INJECTIONS OF HYPERTONIC SALINE

The immediate increase in peripheral pulse amplitude following the intravenous injection of hypertonic saline solution is easily demonstrated with the oscillogram. Instead of the 5 per cent solution ad-



tant in this condition. Again, cleanliness is essential. Gentle irrigation of the part, even when the gangrene is of minimal extent, should be a daily procedure.

Warm boric acid solution is excellent for the purpose, or a solution of azochloramide (1:3300) in saline may be preferred for its antiseptic action. Following the irrigation, the type of dressing will depend upon the nature of the local process. If there is no gross pus formation, boric acid ointment will be adequate. If there is considerable infection along with the gangrene, a wet dressing is preferable, using a solution of either boric acid or of azochloramide in saline. If the process becomes localized and under control, persistence in the daily dressing and a maximum of patience will usually yield gratifying results. While the heel lesions are as a rule extremely painful, much comfort can be obtained from a careful, comfortable dressing, properly applied.

Trauma is notorious as the cause of many cases of diabetic gangrene. Here again prevention is the important feature. Every known diabetic with deficient circulation should be warned, threatened, or even frightened in regard to the danger of home surgery such as cutting corns, calluses, or ingrown nails. Even the ordinary practice of trimming toenails should not be left in the hands of ignorant patients. The physician should not consider it beneath his dignity to properly perform this minor procedure for any patient with diabetes and arteriosclerosis.

Quite often it is not the patient who is to blame for an ill-advised ingrown toenail operation with its disastrous consequences. The physician is often at fault. Careful examination of the peripheral arterial circulation in a diabetic before undertaking any operative procedure on the extremity is absolutely imperative. The simple test for plantar ischemia<sup>1</sup> which I have described will readily disclose any deficiency in the arterial circulation of the lower extremities.

#### COLLATERAL CIRCULATION

Aside from the influence of infection, the progress and ultimate extent of the gangrenous process will depend primarily upon the adequacy of the collateral circulation that has either previously been established or is in the process of formation during treatment. Naturally, the extent of the existing collateral is of considerable consequence. For this reason, the intensive treatment of diabetic arteriosclerosis before the onset of gangrene should be carried out with much greater energy than is the present practice. Routine examination of the arterial circulation should be considered just as important as urine and blood sugar tests in the diabetic adult. The immediate institution of treatment directed to the stimulation of collateral circulation in such cases will, I feel sure, ultimately reduce the number

As mentioned previously, diabetic gangrene may limit itself to one or more toes, or to a restricted area of the heel or dorsum of the foot. In such cases, spontaneous separation of the gangrenous parts can occur with subsequent healing of the resultant ulcer. Unfortunately, however, this does not occur with as great frequency as in thromboangiitis obliterans, where this is the rule rather than the exception. When, in diabetic gangrene, the gangrenous process continues to spread to important parts of the foot or involves the entire foot, en masse, amputation must be performed. In this progressive type of case, the pain is practically uncontrollable because of the comparatively large areas of tissue involved in the mortifying process. Peripheral nerve section will not influence this type of pain. Furthermore, operative incisions in the leg are not entirely without danger in diabetic gangrene. Where the gangrene is limited to one or more toes, the pain is negligible and usually subsides completely as soon as the line of demarcation is established.

*Infection.*—This is by far the commonest indication for amputation in diabetic gangrene.

The situation here is again quite different from that in thromboangiitis obliterans. In the latter, gross infection of the gangrenous parts is entirely harmless and rarely extends into the adjacent healthy tissues. In the diabetic arteriosclerotic, however, a limb with a minimum amount of gangrene must often be sacrificed because of uncontrollable infection.

Even in cases with so-called dry gangrene of a single toe it is important to take all precautions in the prevention of infection. Daily irrigation of such parts with warm boric acid solution, as described previously, followed by the application of a mild antiseptic such as picric acid or mercurchrome particularly along the line of demarcation, is necessary. A sterile dry gauze dressing is imperative. Sometimes, in spite of all precautions, a dry gangrene of the toe changes with alarming rapidity into a rapidly spreading infection of the foot and leg. A very common route of infection is into the plantar tissues and along the tendons or fascial spaces. There may be no immediate rise of temperature to herald the approach of this infection; pain may not be increased. The only evidence of such extension may be exquisite tenderness at the base of the gangrenous toe, along the line of the tendon. In the more advanced cases, gentle pressure at this point will cause the extrusion of a drop of thick pus from the proximal part of the line of demarcation. Careful judgment is essential at this time if the limb is to be conserved. If convinced of the presence of pus in the plantar tissues, immediate incision and drainage are in order. This must be done under general anesthesia and the incision should be planned very carefully to avoid opening uninfected tendons or

vocated in thromboangiitis obliterans, I have used weaker solutions (2 per cent and 3 per cent) in the treatment of diabetic gangrene and believe that they have definitely contributed to the successful outcome of many cases.<sup>2</sup> An additional advantage in the use of hypertonic saline solution in diabetic gangrene is its tendency to lessen the blood sugar, as observed by Glass and Beiless (1930)<sup>3</sup> and Thompson and McQuarrie (1934).<sup>4</sup>

If there are no contraindications, such as a poor myocardium, severe nephritis, or hypertension, saline injections may be given three times a week. In younger patients 300 c.c. of 3 per cent sodium chloride solution suffices, while in older individuals (over 60) 200 c.c. of 2 per cent saline solution will, in most cases, produce an increase in peripheral pulse amplitude, with consequent stimulation of collateral circulation.

#### MECHANICAL APPARATUS

The use of mechanical aids to improve collateral circulation in arteriosclerotic extremities is attended with considerable danger, particularly in the presence of infection. For this reason the employment of suction and pressure, venous compression, and other forms of mechanical therapy is not recommended in diabetic gangrene. The results reported by others, as well as my own observations, do not as yet warrant the routine use of these mechanical aids in this form of arterial disease. If the suction pressure boot could be so constructed as to affect the entire extremity as high as the pelvis, instead of the lower portion only, some theoretical benefit might be obtained. In their present form, it is questionable whether more than compression and distention of the superficial veins is obtained with the various suction pressure apparatuses now available. The harmful effect of the exercise of intermittent venous compression alone is obvious in infected diabetic gangrene.

#### SYMPATHECTOMY AND GANGLIONECTOMY

The organic basis of the rigid arterial walls characteristic of arteriosclerotic gangrene and the known sparse collateral circulation in this condition preclude the possibility of any benefit from operative interruption of the sympathetic pathways in this malady. I believe this opinion is now generally shared by experienced workers in peripheral arterial diseases.

#### INDICATIONS FOR AMPUTATION

The two chief indications for amputation in diabetic gangrene are (1) uncontrollable spread of gangrene of such extent as to destroy the weight-bearing part of the foot and (2) spreading infection that cannot be controlled by incision and drainage or other surgical measures.

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fascial spaces. Incision, as a rule, should be made in a longitudinal direction, starting at the base of the toe. The involved area should be packed wide open and wet dressings applied.

If the collateral circulation is adequate, such incision and drainage may be successful; if not, gangrene of the incised tissues will usually follow.

Unfortunately, in most of these cases, the plantar infection burrows deeper and may even ascend along the tendons into the leg. At this time the diabetes usually runs wild. The blood sugar rises and the urinary sugar increases in spite of heroic increases in insulin dosage. In most of the cases, insulin appears to have no effect. I believe that in diabetic gangrene a progressively higher insulin requirement is a better indication of spreading infection than a rise in temperature.

If the infection subsides and remains localized with incision and drainage or wet dressings alone, conservative measures aimed at demarcation and removal of the gangrenous parts may be continued. If, however, the infection cannot be checked, even in the presence of minimal gangrene, immediate amputation of the limb is justified.

#### TECHNIC OF AMPUTATION

It seems logical to assume that any case of diabetic gangrene severe enough to require ablation of the extremity should be subjected to that type of operation which has been proved to be safest and simplest. I have had the most gratifying results with simple circular no-flap amputation through the lower third of the thigh. The experience of McKittrick and Root,<sup>5</sup> Eliason and Wright,<sup>6</sup> Kuhns and Wilson<sup>7</sup> bears out this opinion. Plastic operations of various types are objectionable here because of the damaged circulation of the extremity and the presence of diabetes. I favor general anesthesia, particularly cyclopropane, because of the stimulating effect of the greater percentage of oxygen that can be given with this gas.

Thorough preoperative cleansing of the skin at the site of incision is carried out by brisk application of benzine followed by alcohol. Iodine is next applied in the usual manner. No tourniquet is used. A circular incision with an ordinary scalpel is made about two inches above the upper border of the patella. This scalpel is now discarded and a fresh one is used for the deeper tissues. Fascia, muscles, and other soft parts are severed in one plane with precise strokes, avoiding unnecessary trauma as by violent spanging or hacking strokes. All bleeding vessels are clamped at once. At this low level of amputation, the popliteal rather than the femoral artery is encountered in the deep medial portion of the thigh, rather close to the femur. If the pulsation of the artery can be felt, it and the accompanying vein are doubly caught and severed between the clamps. Quite often the pulsation cannot be felt because of calcification or thrombosis or both.

In such a case a hard cord can be palpated, which should be clamped and cut along with the accompanying vein. Having severed all soft parts down to the bone, it is imperative that all bleeding points be



Fig. 3.—Healed diabetic gangrene involving four toes. Gangrene precipitated by exposing foot under a lamp and cradle.

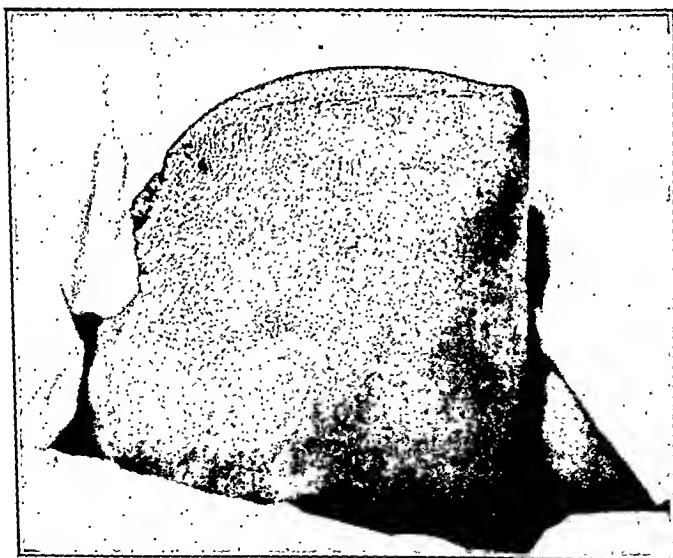


Fig. 4.—Diabetic gangrene. Amputation stump eight days after operation. Primary union.

properly secured before sawing, to avoid later unnecessary trauma incident to hunting for hidden bleeders. A warm saline towel is now spread over the proximal tissues and these are retracted back along the femur by gentle pressure until about two inches of bone is ex-

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sary only in dehydrated patients or in those whose general preoperative care has been neglected for a long time. The average, well-treated diabetic needs no special preparation either before or after the operation.

#### SUMMARY

Arteriosclerosis obliterans plus diabetes is a serious condition requiring intensive treatment as soon as the diagnosis is made.

Prevention of diabetic gangrene is possible if the diagnosis of deficient circulation is made in its incipient stages and proper treatment instituted at once.

Conservative treatment of diabetic gangrene is often successful providing meticulous care is given to the local condition, with due regard for asepsis and antisepsis. Particular attention should be given ringworm infection of the interdigital spaces in diabetes.

Uncontrollable infection or massive, nondemarcating gangrene justifies amputation in diabetic gangrene.

Simple, circular amputation through the lower third of the thigh, with tight closure of the stump and no drainage, is the operation of choice.

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posed. The periosteum of the femur is now cut with a sharp scalpel and scraped distally. The femur is sawed through at this level (about two inches above the line of incision). Frequent changes of towels are essential to maintain a clean operative field at all times.

After proper division of the femur, the soft parts, after removal of all artery clamps and tying of the vessels, should come together with no tension whatsoever over the end of the bone. The muscles are approximated (anteroposterior) with plain catgut sutures. The fascia is closed with plain catgut and the skin edges approximated very carefully with silkworm-gut. No drainage is necessary.

A light dressing is applied to the stump and held in place by adhesive tape. There is no advantage in the use of bulky dressings or clumsy protective devices, such as wood slats or other trimmings. Postoperative elevation of the stump on a pillow is advisable for a few days.

As a rule the temperature falls below 100° F. on the third day. If so, the patient may be out of bed from that time on, a distinct advantage in elderly patients, particularly diabetics. If the stump remains clean, sutures may be removed on the sixth or seventh day and the patient may be discharged from the hospital on the eighth day. Ten days is about the average duration of hospital stay, if primary union has been attained.

If there is evidence of infection in the stump, which is usually superficial, only one or two skin sutures need be removed and a wet dressing applied for a few days. Subsequent healing is usually uneventful.

The advantages of this type of operation over the older methods of leaving stumps wide open or inserting drains are so obvious as to require no comment.

Statistical studies of a series of these cases will be published in a subsequent communication.

#### CONTROL OF DIABETES

During the period of conservative treatment of diabetic gangrene it is necessary to keep the patient reasonably sugar free by the usual methods. The administration of insulin according to frequent examinations of urine during the day is the preferable plan where practicable. It is not necessary to try to maintain the blood sugar and urine absolutely normal throughout the day and night in these patients, who are mostly elderly, but gross carelessness on the part of attendants (if the patient is treated at home) should not be permitted. As mentioned previously, the onset of infection in the foot will call for increasingly larger doses of insulin.

The pre- and postoperative intravenous administration of large amounts of fluid and glucose with sufficient insulin coverage is neces-

"In both cases we found a chronic inflammation. If one looks at the microscopic sections, one sees an infiltration of round cells in normal thyroid tissue which is more or less destroyed by these round cells. The microscopic picture gives no indication of how hard the tumor is. One would expect to find fibrous tissue. However, the predominant finding is round cells. The tissue appears much harder before operation. This must be explained by the numerous dense adhesions to the surrounding structures, especially to the blood vessels, nerves, and trachea. All these adhesions are as dense as leather. They are extremely vascular. One does not make any progress in attempting to loosen the tumor. The great vessels appear to be encased in scar tissue. One can cut them through above and below the tumor, but it is impossible to separate them from the tumor mass. The recurrent laryngeal nerves are embedded in scar tissue and can scarcely be identified. The trachea is so softened that one can imagine it to be already perforated. Even the most malignant tumor is easier to separate than this tissue which is caused by chronic inflammation."

Since Riedel's description of the condition, many cases of this type of thyroiditis have been reported under a wide variety of names, such as primary canceriform inflammation of the thyroid (Tailhefer), primary chronic inflammation of the thyroid (Berry), la thyroidite ligneuse (Delore and Alamartine), benign granuloma of the thyroid (Ewing), lymphadenoid goiter (Williamson and Pearse), and later on simply Riedel's struma.

In 1912, Hashimoto<sup>4</sup> described four cases in which the subjective symptoms were similar to those reported by Riedel, but in which the thyroid tissue was virtually replaced by lymphoid tissue. He called this condition struma lymphomatosa and described differences between this and Riedel's struma. He said in part:

"If we summarize the present clinical observations, we had four patients, all female, all beyond forty years of age, not living in a goitre district and with a family history negative for goitre. . . . They had never been seriously ill, and were without any of the serious infectious diseases frequently followed by disease of the thyroid, especially strumitis. Lues and tuberculosis were excluded clinically. The thyroid enlargement was discovered incidentally in all cases.

"We found a not very rapid enlargement of the thyroid, with good general health. . . . Both lobes were involved in all cases. . . . Severe symptoms of pressure such as dyspnoea and aphonia have never been present. Only in one case, a slight hoarseness appeared before operation combined with incomplete closure of the vocal cords, which can be explained by unsatisfactory function of the arytenoid muscle. Not a trace of inflammation of the thyroid could be found. The mass was freely movable but the consistency was usually so firm that one would think of malignancy or Riedel's strumitis. There was neither regional nor generalized lymphadenopathy. No other visceral abnormality was found.

"The operative findings did not demonstrate much adherence to adjacent structures, as in cases of Riedel's goitre, which is accentuated by this author (Riedel?). Postoperative hoarseness was present in all cases, although slight in amount. In the postoperative course, an edema of the entire body is said to have occurred, disappearing after the internal administration of thyroid. Special attention must be called to the fact that all these cases required a long convalescence before complete recovery, although the usual cases of benign goitre had a postoperative course without complications.

# STRUMA LYMPHOMATOSA (HASHIMOTO)

## A SURVEY OF THE LITERATURE AND REPORT OF A CASE

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VARIOUS forms of chronic thyroiditis have long been known to surgeons and pathologists, and certain types, in which a specific etiologic background can be demonstrated, although sufficiently rare to arouse interest when observed, have ceased to excite more than passing comment. Among these, tuberculous, syphilitic, and parasitic thyroiditis may be mentioned. In certain other types the cause remains undetermined, and although these have been recognized for over forty years as being distinct from the above group, they are still the subject of lively controversy and their status in the nosology of thyroid disease remains to be established.

As far back as 1868, Semple<sup>1</sup> reported a case of "fibroid enlargement of the thyroid body" in a woman fifty years of age. The pathologic description of the autopsy specimen closely resembles that of what is today termed Riedel's struma, but the picture is complicated by the fact that the patient ultimately died of pulmonary tuberculosis.

In 1885, Bowlby<sup>2</sup> described the case of a woman aged forty-two years who died, after a belated operation, of obstructive symptoms from an extensive fibrosis of the thyroid which, in the three years of its known existence, had involved the surrounding structures of the neck and even of the mediastinum but which showed no evidence of remote metastases. In spite of the fact that the tissue looked perfectly benign microscopically and consisted only of dense fibrous tissue, Bowlby felt that its extensive involvement of the surrounding structures was evidence of malignancy, and he tentatively reported it as an infiltrating fibroma or sarcoma of the thyroid.

Eleven years later Riedel<sup>3</sup> described a case of chronic thyroiditis in a man aged forty-two years, which he had preoperatively mistaken for a carcinoma, and in which he had been agreeably surprised to see his patient recover after resection of a small fragment. Microscopically, the picture was one of chronic inflammation with extensive fibrosis and he called the condition Eisenharte strumitis or iron-hard strumitis, and subsequently reported a number of similar cases. One of these, in a child four years of age, is the youngest case on record. His first report included two cases and he summarized the findings as follows:

In analyzing these cases he did not find a marked difference in age incidence, the average for Riedel's disease being 42.8 years and for Hashimoto's struma, 47.6 years. His youngest case of the latter was a woman aged twenty-six. In Riedel's struma the sex distribution was 32 per cent males and 68 per cent females, while in Hashimoto's struma the proportion was 96 per cent females to 4 per cent males, the latter representing the single case reported by Meeker (*vide supra*).

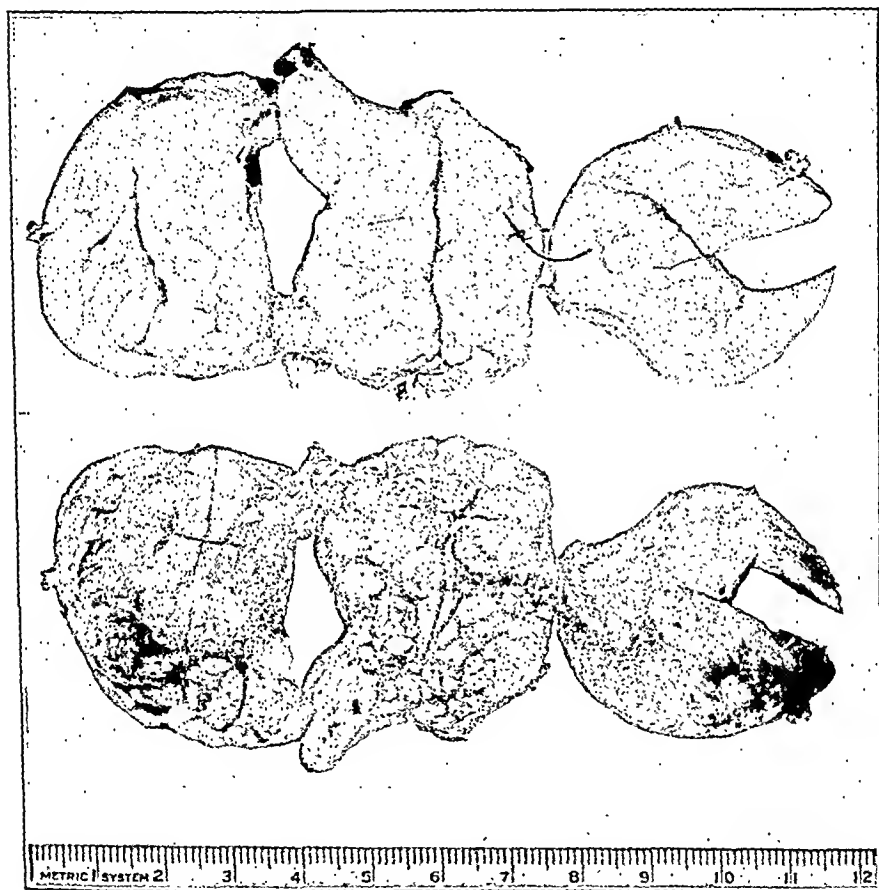


Fig. 1.—Photograph of the gross specimen after formalin fixation.

Various other observers, in analyzing collected cases, report a slightly higher age incidence in Hashimoto's struma, namely, 52.4 years (Graham<sup>12</sup>), 53.0 years (Gilchrist<sup>13</sup>), and 55.5 years (Clute, Eckerson, and Warren<sup>14</sup>), while in Riedel's struma the general average is 40.9 years.

The duration of symptoms at the time of first observation is, if anything, slightly longer in Hashimoto's struma than in Riedel's disease. The average duration in the former is twenty-five months and in the

"The chief (histologic) findings in all cases were:

- "1. Formation of numerous lymphatic follicles.
- "2. Striking changes in the epithelial tissue of the acini (atrophy) of the thyroid and their contents (absence of colloid).
- "3. Extensive proliferation of connective tissue, and diffuse round cell infiltration (lymphocytes and plasma cells)."

Williamson and Pearse,<sup>5</sup> in 1929, expressed the opinion that the condition represents a pathologic variant of a normal function of the thyroid, namely, the elaboration of what they term a lymphogenic secretion. On the basis of McCarrison's<sup>6, 7</sup> work on vitamin A deficiency in albino rats and his experimental production of a picture closely simulating human lymphadenoid goiter by means of an iodine-containing but vitamin-deficient diet, they postulated that this might play a part in the human disease but offered no supporting evidence. They contended that there is a close relationship between Riedel's struma and Hashimoto's struma.

That this is an untenable view is pointed out by Joll<sup>8</sup> and Graham and McCullagh<sup>9</sup> for the following reasons:

1. Hashimoto's struma is confined almost entirely to women over the age of forty-five years, while Riedel's disease usually occurs in adults, but may appear at any age, and men are nearly as often affected as women.
2. Regardless of operative treatment, patients with lymphadenoid goiter tend to develop myxedema, frequently preoperatively. Riedel's disease, even after extensive resection, rarely leads to defective function.
3. Lymphadenoid goiter is a diffuse condition from the outset, and no part of the gland escapes. Localization to a lobe or part of a lobe is common in Riedel's struma.
4. Widespread formation of delicate connective tissue is characteristic of the late stages of lymphadenoid goiter, while dense fibrosis, comparable to scar tissue or keloid formation, is found even in the earlier stages of Riedel's disease.

In regard to incidence, only one case which might be taken for Hashimoto's struma has ever been reported in a man. However, although this case is frequently quoted in the literature as one of Hashimoto's struma, it was reported by Louise H. Meeker herself, with the corroboration of Ewing, as one of Riedel's struma, and judging from her description and the ten plates included with the article, her diagnosis seems fully justified; and this leaves the reported cases of lymphadenoid goiter confined exclusively to women. In a very comprehensive study published in December, 1935, J. G. Lee<sup>11</sup> was able to collect from the literature only twenty-six cases of Hashimoto's struma, including his own three cases, and ninety cases of Riedel's struma including nine of his own.

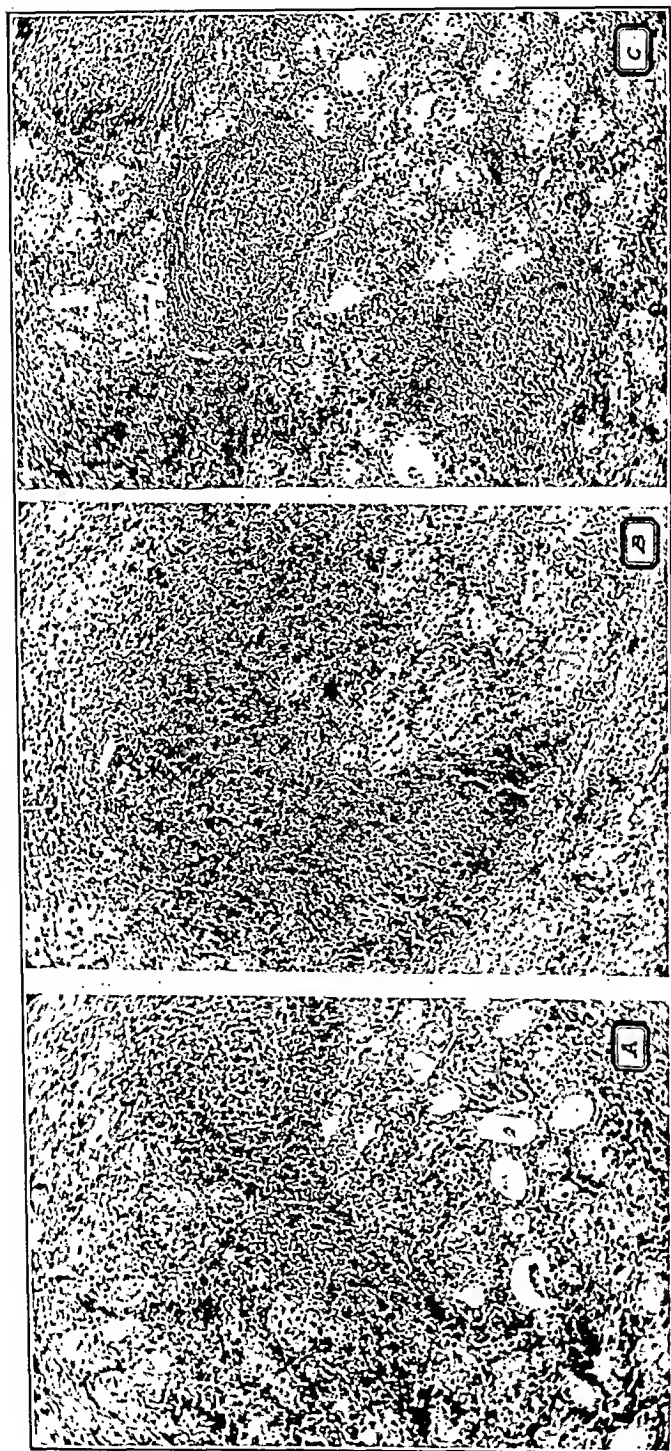


Fig. 2.—Photomicrographs from various portions of the gland, showing generalized lymphocytic infiltration and well-developed germinal centers. (X200)

latter is eighteen months (average from Gilechrist's and J. G. Lee's reports), which militates against the view that Riedel's disease is a late stage of lymphadenoid goiter.

Although no specific figures are available, the occurrence of preoperative myxedema is not reported in any of the cases of Riedel's disease that have been encountered in the literature, while this is a common event in Hashimoto's struma. Postoperative myxedema has occurred in 40 per cent of the cases of lymphadenoid goiter, and in 20 to 25 per cent of cases of Riedel's disease. The tendency of struma lymphomatosa to develop myxedema is strongly emphasized by Hertzler,<sup>15</sup> and eight of the nine cases reported by Clute, Eckerson, and Warren<sup>14</sup> developed myxedema, while the ninth was lost sight of and her later course could not be followed.

In every case of Hashimoto's struma the entire gland has been involved, while in Riedel's struma 30 per cent of J. G. Lee's series, and 49 per cent of Gilechrist's series showed only unilateral involvement. Furthermore, no case of Hashimoto's struma has been reported in which there was involvement of the perithyroid tissues, while 78 per cent of Gilechrist's series and 80 per cent of J. G. Lee's series of Riedel's disease showed cervical adhesions at operation.

The etiology of both conditions remains obscure. The records of the majority of the reported cases are incomplete, but where it is included, a history of some previous infectious disease or the finding of focal infection is quite common in Riedel's struma. Clute and Lahey<sup>16</sup> in 1932 included Riedel's struma in their group of chronic thyroiditis either primary in the gland or secondary to general infection but did not mention Hashimoto's struma. In a later paper, Clute, Eckerson, and Warren noted a possible infectious factor in several of their nine cases of Hashimoto's struma.

The suggestion of dietary deficiency offered by Williamson and Pearse<sup>5</sup> has already been mentioned; and Graham and McCullagh,<sup>9</sup> in addition to infectious diseases and focal infections, consider the factor of antecedent hyperthyroidism as a possible predisposing cause. They point out that although evidence of this cannot always be demonstrated, it is recognized that well-advanced myxedema is not infrequently seen in which there is no history of previous toxicity and yet the pathologic picture is that of a burned-out, toxic goiter. They consider it premature, therefore, to rule out hyperthyroidism as a precursor of struma lymphomatosa, with a possible direct relationship.

It becomes evident, therefore, that a careful analysis of a large series of cases in which complete data are available will be necessary if the status of these two diseases of the thyroid is to be established. A survey of the available literature through the end of 1936 adds fifteen cases of Hashimoto's struma to the twenty-six collected by J. G. Lee, making a total of forty-one cases. In most of these, however, insufficient detail is presented to allow a comprehensive analysis.

ritability, there was a dull occipital headache, and she began to notice an occasional swelling of the hands and of the infraorbital region, and this was accompanied by mild tingling and numbness of the hands. At the same time her skin began to become noticeably dry. There was mild anorexia and constipation, but no loss of weight, and the patient noticed that she felt cold all the time. She had never noted excessive perspiration at any time, and the only symptom referable to her heart was a mild palpitation on moderate exertion. Obstructive symptoms were absent. For about a year previous to admission the patient had been under the care of her family physician, who had been treating her with Lugol's solution, but no B.M.R. determination had been made. She was able to carry on her work until a week before admission but then retired to bed and was sent to the hospital by her physician.

**Past History:** The patient had the usual childhood diseases, but except for an attack of multiple furunculosis eight years previously and several mild attacks of right upper quadrant pain, nausea, vomiting, and slight transient jaundice, her general health had been good.

**Family History:** This was essentially negative except that her father had died of "dropsy" at the age of sixty.

On admission T.P. and R. were 98.6, 98, and 18. B.P. 154/90. Patient was well developed and nourished and did not appear acutely ill. Her skin was dry and thick, especially over the hands, and there was an appreciable thickening and enlargement of the tongue. The thyroid was moderately enlarged, the right lobe slightly larger than the left, and quite firm, but not appreciably nodular. Hgb. 76%; R.B.C. 4.78; W.B.C. 8,700; Schilling count—Myelo. 2%; PMN 78%; Lymph. 18%; LMN 1%; Eos. 3%. Urine negative, Wassermann not reported. B.M.R. -13%.

Under a diagnosis of toxic diffuse goiter with involution, a subtotal thyroidectomy was done, and at operation the gland, which was removed without difficulty, was found to be smooth, pale, and rather firm.

Postoperative course was uneventful except that on the third day she had a mild attack of right upper quadrant pain, with some tenderness, and mild nausea and vomiting. Two attempts at gallbladder visualization showed total absence of shadow. The attack subsided promptly, and the patient was discharged on daily doses of thyroid extract.

The pathologic report was as follows: "This specimen consists of two rounded masses of tissue identified as thyroid gland. They are joined by a slender capsular strand, and only a small portion of the isthmus is included. The right lobe measures  $5\frac{1}{2}$  by  $3\frac{1}{2}$  by 2 cm., and the left, 5 by  $3\frac{1}{2}$  by 3 cm. There are no grossly apparent nodulations and both masses are well encapsulated. The cut surface presents a rather pale, pinkish appearance and is homogeneous throughout. There is no grossly visible colloid and the cut surface is smooth and unbroken by visible fibrous septa. On microscopic examination sections from various portions of both lobes show an identical picture. The most striking feature is an extensive infiltration of the entire tissue by lymphocytes, and numerous secondary nodules, complete with germinal centers, are present. The acini are uniformly small and contain little or no colloid. Such colloid as is present stains poorly and much of it is basophilic. The lining epithelium of the acini shows cells which are pale and swollen, and in many the cells fill the entire lumen. Thus the lining epithelium appears very inactive and the pattern certainly does not suggest formation of any new acini. The capsule of the gland is dense and somewhat thickened, but the massive infiltration of lymphocytes is confined within the parenchyma of the gland, and there is no evidence of extension of the process through the capsule. The connective tissue in the gland appears swollen and degenerated, and much of it is becoming hyalinized."

**Diagnosis:** Struma lymphomatosa (Hashimoto).



The condition is so unusual that the accumulation of a considerable series in any one clinic is a prolonged process and it is to be hoped that sufficient cases will be reported in the next few years to make such an analysis possible. With this in mind, the present case is recorded in some detail.

CASE REPORT.—The patient, Mrs. A. F., was a white woman aged fifty years and a gravida ii, para ii, four years past the climacteric. She was admitted to the

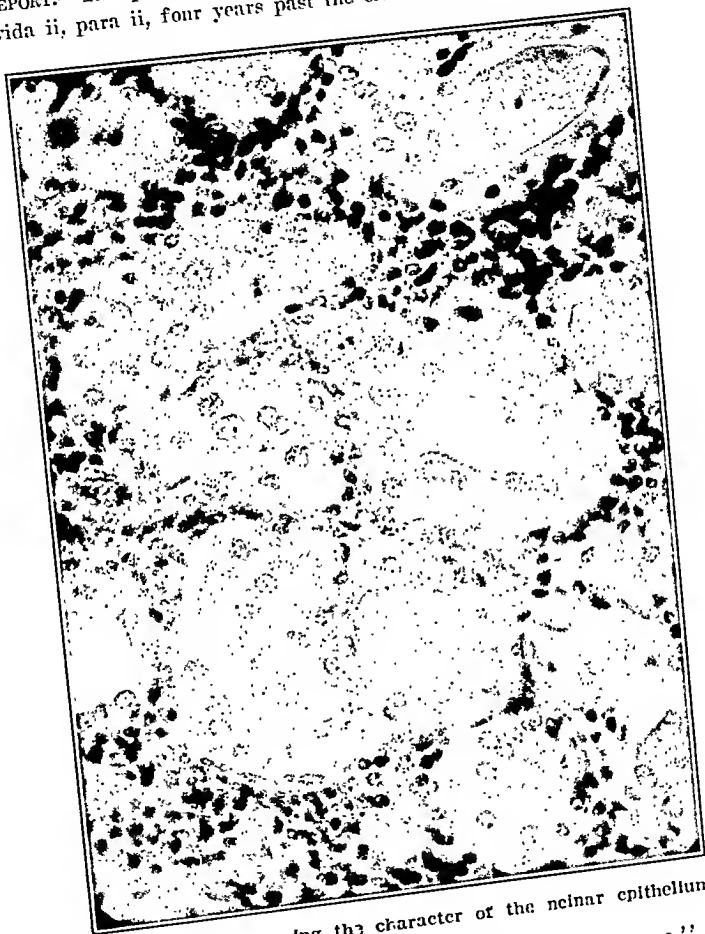


Fig. 3.—Photomicrograph showing the character of the nuchal epithelium. ( $\times 800$ )

hospital October 29, 1936, with a chief complaint of "nervousness." She dated the onset of her present illness from an attack of "influenza" two years previously. She knew at that time that she had a goiter but was not sure how long she had had it, and as far as she knew, it had never given her any symptoms. After recovery from the influenza she began having attacks of nervousness, which seemed to be intermittent, and during which she was extremely irritable and felt, herself, that she had appreciable personality changes. This condition continued without notable change and without increase in the size of the goiter for about a year. In February, 1936 (six months before admission), she had another attack of influenza, after which all of her symptoms were exaggerated. During an attack of nervousness and ir-

# THE SHOCK SYNDROME IN LIVER PERITONITIS

## AN INTERPRETATION OF THE RÔLE DOG LIVER BACTERIA PLAY IN CAUSING RAPID DEATH

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THE possible formation of toxic substances by autolysis of body tissues is an old problem which has been intensively studied. Renewed interest was aroused by the investigations of Mason, Davidson, Matthew and Rastello,<sup>1</sup> who reported that autolysis of dog liver in vivo was highly toxic and caused rapid death. The numerous investigations which were stimulated by this observation have resulted in the advancement of different theories to explain the rapid death which follows intraperitoneal implantation of liver and bile salt preparations. Ellis and Dragstedt<sup>2</sup> reported experiments to show that the rapid death of the animal was intimately associated with an anaerobic bacterial peritonitis caused by bacteria which normally inhabit the adult dog liver. Andrews, Rewbridge, and Hrdina<sup>3</sup> concluded from their experiments that the adult dog liver as well as other tissues harbored the Welch bacillus and attributed rapid death to a Welch bacillus toxemia. Dvorak,<sup>4</sup> likewise, concluded that death was caused by exotoxins produced by dog liver bacteria which grew in the autolyzing liver fragments. We have been interested in this problem for a number of years and in our early studies<sup>5, 6</sup> we presented experiments to show that the bacteria recovered from the tissues of the dog produced no exotoxins. Furthermore, we demonstrated that the dog liver anaerobe differed from the Welch bacillus both in morphology and cultural characteristics. In a recent publication,<sup>7</sup> we showed that dogs subjected to intraperitoneal implantation of fresh, ground, adult dog liver die rapidly with all the laboratory and clinical signs of severe shock. Death was associated with an anaerobic bacterial peritonitis. We found, however, that if fresh liver was ground with an equal quantity of salt solution and strained so that the gross connective tissue elements were removed, the resulting suspension of liver cells was much less toxic than the whole liver. When these cellular elements of fresh dog liver were placed intraperitoneally, the animal survived even though considerable amounts of the liver substance remained unabsorbed for several days. On the contrary, when equivalent amounts of blood vessel, bile duct, and connective tissue elements of liver, or

## COMMENT

An interesting feature of the case is that it presents two of the three aspects mentioned above in connection with possible etiologic relationships. Not only is there a history of two attacks of influenza and one of multiple furunculosis, but there was strong evidence of a focus of infection in the gallbladder. Moreover, her history and clinical course indicate a definitely toxic thyroid on which unmistakable signs of myxedema were superimposed.

Although Ewing states that struma lymphomatosa is an early stage of Riedel's disease, Graham's objections to this view are unquestionably impressive. While the former disease may occur in considerably younger persons than Graham's survey indicated, the tendency is certainly toward a higher incidence in older women, and this and the longer average duration of symptoms must bear some weight in a consideration of the disputed relationship between the two diseases. Moreover, in Hashimoto's struma the diffuse character of the lesion, its limitation to the gland parenchyma without extrathyroidal adhesions, its common association with myxedema, and its apparent limitation to female patients are in quite striking contrast to the usual course of Riedel's disease. These features together with the rather distinctive microscopic findings in the two conditions leave one with the impression that they must be regarded as separate entities.

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in some manner associated with the growth of dog liver bacteria in the peritoneal cavity. In this preliminary experiment, bacteriologic studies on peritoneal exudate and blood chemical analyses were not attempted.

EXPERIMENTS UPON FRESH, GROUND ADULT DOG LIVER  
STERILIZED BY AUTOCLAVING

Ellis and Dragstedt,<sup>2</sup> Dvorak,<sup>4</sup> and others have reported that autoclaved fresh, adult dog liver does not kill when placed intraperitoneally. However, if the sterilized liver is infiltrated with dog liver bacteria before it is placed intraperitoneally, it does kill. We likewise reported that autoclaved fresh liver failed to kill unless it was con-

TABLE III

THE PHYSICAL AND CHEMICAL CHANGES IN THE BLOOD OF DOGS SUBJECTED TO  
INTRAPERITONEAL IMPLANTATION OF FRESH, GROUND, ADULT DOG  
LIVER STERILIZED BY AUTOCLAVING

BLOOD STUDIES	*DOG 278—WT. 13 KILO.		*DOG 279—WT. 17 KILO.	
	NORMAL	AT 15 HR.	NORMAL	AT 15 HR.
R.B.C.	4,830,000	7,130,000	8,950,000	10,900,000
W.B.C.	12,000	8,650	21,700	8,650
Coagulation time	1' 30"	40"	1' 30"	50"
Hemoglobin—gm. per 100 c.c.	12.5	16	14.5	17
CO <sub>2</sub> vol. %	57	} ----	53	43
Hematocrit—% cells	47		53	30
Per cent plasma	53		47	20
Plasma volume in c.c.	635		565	220
Blood volume in c.c.	1,200	} ----	1,200	1,100
Blood sugar—mg. per 100 c.c.	138		74	81
Total N.P.N.—mg. per 100 c.c.	36	62	33	80
Total N. (as protein) gm.	10	12.8	10.6	14.2
Blood chlorides—mg. per 100 c.c.	495	466	495	451

\*Dog 278 was given 200 gm. of liver (15.4 gm. per kilo.). Dog 279 was given 100 gm. of liver (5.9 gm. per kilo.).

†Since dog 278 received a large amount of liver intraperitoneally (15.4 gm. per kilo.), we wished to see if he would survive, so we did not do blood volume studies or determine the CO<sub>2</sub> capacity of the blood plasma. These studies entail the removal of 30 c.c. of blood, which is often fatal to dogs suffering from this degree of shock.

taminated.<sup>6</sup> In this series of experiments we have extended our investigations upon this phase of the problem. On numerous occasions we have observed the marked symptoms of shock manifested by dogs subjected to intraperitoneal implantation of fresh liver sterilized by autoclaving. Although the animals survive, they are nevertheless prostrated and acutely ill for a number of hours. The blood pressure is very low, the extremities are cold, and the pulse is weak and thready. Our next experiment was undertaken to ascertain the physical and chemical changes in the blood of dogs subjected to intraperitoneal implantation of fresh, ground adult dog liver sterilized by autoclaving.

*Experiment 3.*—Livers were removed from sacrificed dogs, ground, and sterilized by autoclaving. The liver substance was introduced

gm. were introduced the dogs sterilized the peritoneal cavity and survived. On this series of animals the lethal amount of cellular elements was in excess of 7 gm. per kilo. of the animal's weight. When less than this amount was introduced, the animals survived but manifested varying degrees of shock. Taking the concentration of blood as an index of the degree of shock, it can be seen that animals subjected to 5 to 6 gm. of cellular elements per kilo. were in a more critical condition than those receiving 2 to 3 gm. per kilo.

In all our studies upon fresh, adult dog liver, the rapid death of the animal has been associated with anaerobic bacterial peritonitis. In our next experiment, an attempt was made to increase the peritoneal resistance of the dog before subjecting the animal to known lethal amounts of fresh, ground dog liver.

TABLE II

THE PROTECTIVE EFFECT OF STEINBERG'S TRAGACANTH VACCINE AGAINST DEATH  
DUE TO DOG LIVER PERITONITIS

PROCEDURE	DOG	AMOUNT OF FRESH, GROUND, ADULT DOG LIVER PLACED INTRA- PERITONEALLY		RESULT
		TOTAL GM.	GM. PER KILO. OF ANIMAL'S WEIGHT	
Unvaccinated animals	199	100	7.00	Died in 15 hr.
	200	100	5.90	Died in 15 hr.
	201	50	3.56	Died in 12 hr.
	202	50	2.60	Died in 15 hr.
Peritoneal immunity increased by intraperitoneal injection of 30 c.c. of Steinberg's tragacanth vaccine 24 hours before the in- troduction of liver.	203	100	7.60	Survived
	204	100	7.60	Died in 15 hr.
	205	50	3.85	Survived
	206	50	3.33	Died in 72 hr.

*Experiment 2.*—Eight dogs were used. Four animals were given prophylactic intraperitoneal injections of Steinberg's tragacanth vaccine\* and four were untreated. Twenty-four hours later the animals were subjected to intraperitoneal implantations of varying amounts of fresh, ground adult dog liver. Two of the protected animals each received 100 gm. of liver and the remaining 2 each received 50 gm. Two of the unprotected dogs each received 100 gm. of liver and the remaining 2 each received 50 gm. Table II shows the results of the experiment.

Our studies on this phase of the problem are only preliminary but the above experiment indicates that dogs can be protected against death due to liver peritonitis by increasing the peritoneal resistance. We believe this observation supports the concept that rapid death is

\*The protective effect of this vaccine has been demonstrated in dogs receiving Steinberg's peritonitis-producing mixture. (Steinberg, B., and Goldblatt, H.: Protection of Peritoneum Against Infection, *Surg., Gynec. & Obst.* 47: 15, 1933.)

TABLE I  
THE EFFECT OF PLACING VARYING AMOUNTS OF THE CELLULAR ELEMENTS OF FRESH, ADULT DOG LIVER INTRAPERITONEALLY

THE EFFECT OF PLACING VARYING AMOUNTS OF LIVER CELLULAR EXUDATE IN THE PERITONEAL CAVITY												
DOG	AMOUNT OF CELLULAR ELEMENTS PLACED INTRAPERITONEALLY		RESULT	BLOOD ANALYSES						PERTONEAL EXUDATE REMOVED 18 HOURS AFTER INTRODUCTION OF LIVER		
				NORMAL			18 HOURS AFTER INTRODUCTION OF LIVER					
				R.B.C. MILLION PER C.M.M.	Hb.	T.N.P.N.	R.B.C. MILLION PER C.M.M.	Hb.	T.N.P.N.			
54	140	14.0	Died in 22 hr.	6.55	13.0	25.0	9.45	18.0	38.0	Positive for dog anaerobe	Positive for dog anaerobe	CULTURE
55	140	13.5	Died in 19 hr.	5.70	13.5	21.6	8.20	19.0	70.0	Positive for dog anaerobe	Positive for dog anaerobe	
56	100	7.5	Died in 30 hr.	7.20	13.0	29.0	7.44	17.0	48.0	Positive for dog anaerobe	Positive for dog anaerobe	
57	100	6.3	Survived	8.40	14.0	34.0	9.55	16.5	37.0	Negative	Negative	
60	100	5.3	Survived	7.00	14.0	26.0	7.20	16.0	31.0	Negative	Negative	Positive after 3 days' incub.
62	100	6.3	Survived	6.50	13.5	13.6	7.00	15.0	25.8	Negative	Negative	Positive after 3 days' incub.
273*	70	2.5	Survived	7.00	13.0	40.0	7.40	13.0	46.0	Negative	Negative	Positive after 3 days' incub.
274*	70	3.2	Survived	6.88	13.0	30.0	7.32	13.5	36.0	Negative	Negative	Positive after 3 days' incub.

\*The data on dogs 273 and 274 are reported in detail in a previous paper. They are included in this paper for the purpose of correlation.

†We interpret the fact that these cultures were positive after three days' incubation as evidence that the peritoneal exudate of these animals contained viable spores although the dogs had apparently destroyed the vegetative forms of bacteria. Although no subsequent cultures were taken of peritoneal exudate, the complete recovery of the dogs would indicate that the peritoneal cavity eventually became sterile.

the whole liver substance were placed intraperitoneally the animal rapidly died with severe shock associated with anaerobic bacterial peritonitis.

We have extended our experiments upon fresh dog liver and have also investigated the effects of placing intraperitoneally various preparations of fresh liver sterilized by autoclaving as well as different preparations of incubated liver. In the following experiments we will present observations which may explain many of the conflicting reports of different investigators. We also submit what, in our opinion, may be the correct interpretation of the rôle played by dog liver bacteria in causing rapid death. Since we used different groups of liver preparations in our studies we shall present our experiments under these leads.

#### FURTHER EXPERIMENTS UPON FRESH, GROUND, ADULT DOG LIVER

All investigators of this problem agree that when 30 or more grams of fresh, adult dog liver are placed intraperitoneally the animal dies, usually within 24 hours. When this quantity is used, the amount per kilogram of the animal's weight has little influence upon the time of survival. In a previous paper,<sup>7</sup> we reported that the cellular elements of liver were less toxic to the experimental animal than equivalent amounts of whole liver, or the blood vessel, bile duct, and connective tissue fraction. The amount of cellular elements used in these earlier experiments was approximately 70 gm. In the following experiment an attempt was made to ascertain the minimal amount of cellular element of fresh liver which would cause rapid death when placed intraperitoneally.

*Experiment 1.*—The cellular elements were prepared as described previously<sup>7</sup> and varying amounts placed intraperitoneally in 6 dogs through a small laparotomy incision. Two dogs each received approximately 140 gm. of cellular elements together with equal volumes of normal saline. The remaining four animals each received approximately 100 gm. of cellular elements together with 100 c.c. of normal saline. Blood counts, hemoglobin determinations, and total nonprotein nitrogen estimations were done on samples of blood removed before the liver substance was administered and repeated 18 hours later. Samples of peritoneal exudate were removed from each of the animals 18 hours after the introduction of liver for bacteriologic smear and culture. Table I shows the results of the experiment.

The experiment demonstrates that the nontoxicity of the cellular elements of liver is relative, and apparently depends upon bacterial growth in the peritoneal cavity. When more than 100 gm. of cellular elements were introduced, the dogs developed bacterial peritonitis and died within 30 hours with shock findings similar to those seen when animals are given lethal amounts of fresh, whole liver. When less than 100

TABLE IV

THE EFFECT OF PLACING AUTOCLAVED CELLULAR ELEMENTS OF FRESH, ADULT DOG LIVER INTRAPERITONEALLY AFTER INFILTRATING THE LIVER MATERIAL WITH LIVING CULTURES OF DOG LIVER BACTERIA

DOG	AMOUNT OF AUTOCLAVED CELLULAR ELEMENTS PLACED INTRA-PERITONEALLY			BLOOD STUDIES				PERITONEAL EXUDATE REMOVED 15 HR. AFTER INTRODUCTION OF LIVER		RESULT
	TOTAL GM.	GM. PER KILO.		NORMAL		AFTER 15 HR.		SMEAR	CULTURE	
				R.B.C. MILL. PER C.MM.	H.B.	R.B.C. MILL. PER C.MM.	H.B.			
<i>Autoclaved Cellular Elements Infiltrated With Dog Liver Bacteria</i>										
288	70	4.00		5.37	13.0	7.42	15.0	Negative	Pos. after 3 days' incubation	Survived
289	70	4.40		6.30	12.5	9.11	15.5	Negative	Pos. after 3 days' incubation	Survived
287	100	6.45		6.50	13.0	10.10	17.0	Positive	Pos. in 8 hr.	Died in 9 days
<i>Sterile, Autoclaved Cellular Elements</i>										
290	70	3.2		7.70	14.5	9.45	16.5	Negative	Negative	Survived
291	70	3.7		7.37	13.0	10.47	16.5	Negative	Negative	Survived
292	100	5.3		6.40	15.0	6.37	16.0	Negative	Negative	Survived
293	100	6.6		6.41	15.0	7.84	16.0	Negative	Negative	Survived



intraperitoneally through a small laparotomy incision with equal volumes of sterile normal saline. Two dogs were used in the experiment. One of the animals received 100 gm. of liver plus 100 c.c. of normal saline, the other 200 gm. plus 200 c.c. of saline. Physical and chemical analyses were made on the blood before the liver was placed intraperitoneally and repeated 15 hours later in the same manner described in a previous publication.<sup>7</sup> The results of the experiment are given in Table III.

The experiment supports the clinical observation that animals subjected to intraperitoneal implantation of this preparation of liver suffer a marked degree of shock. Within a few hours after introducing the liver, both animals were prostrated. Table III shows the marked concentration of blood, loss of plasma volume, and increased total nonprotein nitrogen. We have frequently observed that the loss of a small amount of blood is fatal to such animals. We were not surprised, therefore, when dog 279 died following the removal of 40 c.c. of blood necessary for complete chemical studies. Since we wished to see if dog 278 would survive, only 10 c.c. of blood were removed, and the hematocrit and blood volume determinations were not done. This animal survived even though he was subjected to 200 gm. of liver (15.4 gm. per kilo.). The changes in the blood and the general appearance of the animal indicated a condition of shock comparable to that shown by dog 279 which died following the removal of 40 c.c. of blood.

In Experiment 1, we observed that the cellular elements of fresh ground liver are relatively nontoxic. In our next experiment we attempted to ascertain whether autoclaving the cellular elements of fresh dog liver would influence this result.

*Experiment 4.*—In this experiment an attempt was made to see if autoclaved cellular elements, infiltrated with a living culture of dog liver bacteria, would cause rapid death when placed intraperitoneally. Seven dogs were used. Each was given autoclaved cellular elements of fresh, adult dog liver intraperitoneally plus equal volumes of sterile normal saline. Each of three of the animals received varying amounts of liver material which had been infiltrated with 1.5 c.c. of a growing culture of dog liver bacteria just prior to its introduction intraperitoneally. The other four dogs were given varying amounts of sterile, autoclaved cellular elements. Since we wished to see if the animals would survive, extensive blood analyses were not attempted. A small sample of blood was removed from each animal for red cell count and hemoglobin estimation before the liver was introduced and additional samples were removed 15 hours later. The results of the experiment are given in Table IV.

TABLE V  
THE EFFECT OF PLACING VARYING AMOUNTS OF FRESH, GROUND, AUTOCLAVED ADULT DOG LIVER INTRAPERITONEALLY AFTER INFILTRATING THE LIVER MATERIAL WITH DOG LIVER BACTERIA

DOG	AMOUNT OF AUTOCLAVED LIVER INTRODUCED INTRAPERITONEALLY			BLOOD STUDIES				PERITONEAL EXUDATE REMOVED 1, 2, AND 4 DAYS AFTER THE INTRODUCTION OF LIVER		RESULT
				NORMAL		AFTER 96 HR.				
				R.B.C. MILL. PER C.MM.	H.B.	R.B.C. MILL. PER C.MM.	H.B.			
	<i>Fresh, Autoclaved Dog Liver Infiltrated With Dog Liver Bacteria</i>									
307	70	4.0	6.35	13.0	8.45	15.5	All pos.	All pos.	Died in 9 days	
308	100	6.0	6.47	13.5	9.00	17.0	All pos.	All pos.	Died in 5 days	
<i>Fresh, Sterile, Autoclaved Adult Dog Liver</i>										
306	70	4.0	6.80	14.0	9.30	16.5	Negative	Negative	Survived	
305	100	7.5	5.80	12.5	8.20	16.0	Negative	Negative	Survived	

All of the animals manifested general symptoms and laboratory signs of shock, but all but one survived. Dog 287 died on the ninth postoperative day with anaerobic bacterial peritonitis. This animal was subjected to 100 gm. of autoclaved cellular elements which had been infiltrated with 1.5 c.c. of a growing culture of dog liver bacteria. Bacteriologic smears made of peritoneal exudate removed from this animal 15 hours, 2 days, 4 days, and 6 days postoperative were all positive for the dog liver anaerobe. Bacteriologic smears taken of samples of peritoneal exudate removed from the other 6 dogs 15 hours after the introduction of liver were negative for vegetative forms of bacteria. However, cultures taken of the peritoneal exudate removed from dogs 288 and 289 were positive for the dog liver anaerobe after 3 days' incubation. We interpret this observation as evidence that the peritoneal exudate of these two animals contained viable spores although the dogs had apparently destroyed the vegetative forms of bacteria.

We find in Table IV that when less than 100 gm. of autoclaved cellular elements were used, two dogs (288 and 289) survived even though the liver preparation was infiltrated with a growing culture of dog liver bacteria. Dog 287, however, was unable to survive 100 gm. of this material, dying in 9 days with peritonitis. The 9-day interval is of interest because of the fact that fresh, raw liver, when given in lethal amounts, always kills in a much shorter time, usually within 24 hours. It appears that autoclaving the liver substance causes decreased toxicity even though the preparation is inoculated with growing cultures of liver bacteria. As an additional check on this observation we carried out Experiment 5.

*Experiment 5.*—In this experiment we used whole liver ground with equal quantities of salt solution and sterilized by autoclaving. (The connective tissue portions were not removed.) Four dogs were given different amounts of this preparation. In two dogs (307 and 308) the liver preparation was infiltrated with 1.5 c.c. of a growing culture of dog liver bacteria just prior to its introduction intraperitoneally. Samples of blood were removed for red cell counts and hemoglobin determinations before the liver material was introduced, and the analyses repeated 96 hours later. Bacteriologic smears and cultures were taken of samples of peritoneal exudate removed from the animals 1, 2, and 4 days postoperative. The results of the experiment are given in Table V.

A few hours after the intraperitoneal introduction of liver, all four animals showed general signs of severe shock. Red cell counts and hemoglobin determinations made 96 hours after the introduction of liver showed that all the animals were still suffering from shock.

Table V shows that the 2 animals which received sterile, autoclaved liver had no bacteria in the peritoneal cavity, while the 2 animals

TABLE V

THE EFFECT OF PLACING VARYING AMOUNTS OF FRESH, GROUND, AUTOCLAVED ADULT DOG LIVER INTRAPERITONEALLY AFTER INFILTRATING THE LIVER MATERIAL WITH DOG LIVER BACTERIA

DOG	AMOUNT OF AUTOCLAVED LIVER INTRODUCED INTRAPERITONEALLY			BLOOD STUDIES						PERITONEAL EXUDATE REMOVED 1, 2, AND 4 DAYS AFTER THE INTRODUCTION OF LIVER		RESULT
				NORMAL		AFTER 96 HR.						
	TOTAL GM.	GM. PER KILO.	R.B.C. MILL. PER C.MM.	H.B.	R.B.C. MILL. PER C.MM.	H.B.	SMEAR	CULTURE				
<i>Fresh, Autoclaved Dog Liver Infiltrated With Dog Liver Bacteria</i>												
307	70	4.0	6.35	13.0	8.45	15.5	All pos.	All pos.	All pos.	Died in 9 days		
308	100	6.0	6.47	13.5	9.00	17.0	All pos.	All pos.	All pos.	Died in 5 days		
<i>Fresh, Sterile, Autoclaved Adult Dog Liver</i>												
306	70	4.0	6.80	14.0	9.30	16.5	Negative	Negative	Negative	Survived		
305	100	7.5	5.80	12.5	8.20	16.0	Negative	Negative	Negative	Survived		

given the bacterial infiltrated liver substance suffered from bacterial peritonitis. These bacteria were the spore-forming anaerobic species commonly found in adult dog liver. Even though these animals suffered from severe shock associated with an anaerobic bacterial peritonitis, they survived, one for more than 9 and the other for more than 5 days after the intraperitoneal introduction of the inoculated liver substance. This observation confirms the finding reported in Experiment 4, that autoclaved dog liver infiltrated with dog liver bacteria fails to cause death as rapidly as equivalent amounts of unautoclaved raw liver. Both these preparations of liver cause death, and death in each instance is associated with the presence of dog liver bacteria in the peritoneal cavity. To attribute the cause of rapid death in dog liver peritonitis to exotoxins produced by dog liver bacteria seems unreasonable in view of the above observation. It seems more logical to assume that rapid death is caused by toxic substances produced by the action of these bacteria upon raw liver substance.

The experiment also demonstrates that the dog cannot sterilize the peritoneal cavity when ground, autoclaved liver (containing the connective tissue portion) is infiltrated with dog liver bacteria and placed intraperitoneally. (See Table V.) When equivalent amounts of autoclaved cellular elements, infiltrated with dog liver bacteria, were placed intraperitoneally, the dog sterilized the peritoneal cavity and survived. (See Table IV.) We believe that this observation is to be explained on the basis that the finely divided cellular elements permit rapid phagocytosis of any bacterial contaminants.

It appears from the above experiments that neither shock alone, nor shock associated with dog liver bacteria peritonitis, is sufficient to explain the cause of rapid death which occurs when fresh, adult dog liver is placed intraperitoneally. Our experiments have indicated that rapid death is associated in some manner with the action of dog liver bacteria upon fresh liver substance. In order to investigate this concept, we studied the effects of placing incubated liver preparations intraperitoneally.

#### EXPERIMENTS UPON DIFFERENT PREPARATIONS OF INCUBATED DOG LIVER

Mason, Davidson, and Rastello<sup>1</sup> were the first to report that incubated dog liver was toxic when placed intraperitoneally. Dvorak<sup>1</sup> concluded that the toxicity of incubated dog liver is due to heat labile exotoxins produced by anaerobic bacteria found in adult dog liver. Andrews and Hrdina<sup>2</sup> reported that the toxic factor found in incubated liver belongs to the peptone proteose group and indirectly kills the experimental animal by causing an idiopathic Welch bacillus infection. In our early experiments<sup>3</sup> we presented evidence to show that incubated dog liver is very toxic and rapidly kills, even though the preparation is autoclaved before intraperitoneal injection. Such

autoclaved, lethal preparations of incubated liver could not have contained any heat labile, bacterial exotoxins. Furthermore, by careful bacteriologic technique, we demonstrated that animals given this sterile preparation of liver die without the invasion of the peritoneal cavity by the Welch bacillus or any other bacteria. We observed that the animals died with general symptoms of severe shock.

Our next experiment was undertaken to ascertain the physical and chemical changes in the blood of dogs subjected to intraperitoneal implantation of incubated adult dog liver sterilized by autoclaving. We also wished to contrast these findings with those manifested by dogs subjected to various preparations of fresh, unincubated liver.

*Preparation of Incubated Liver.*—Livers were removed from sacrificed dogs, using aseptic surgical precautions against contamination. As an added precaution against contamination by extraneous bacteria, the livers were plunged into scalding water until the surfaces were coagulated. The gallbladder, fat, connective tissue, and larger blood vessels were dissected away, and the remaining liver material was passed through a food chopper. The ground liver was divided into 110 gm. portions and placed in 500 c.c. Erlenmeyer flasks together with equal volumes of sterile normal saline solution. The flasks of liver were incubated 3 days at  $37\frac{1}{2}^{\circ}$  to  $40^{\circ}$  C. The flasks of liver were then autoclaved at 15 pounds pressure for 30 minutes and shaken for 50 minutes in a mechanical shaker. This results in a fine division of liver substance and practically all of it strains through six layers of gauze. The strained liver was reautoclaved to insure sterility and placed in the refrigerator until used in the different experiments. The liver substance was handled at all times with sterile technique and every effort was made to prevent contamination by extraneous bacteria.

*Experiment 6.*—Twelve dogs were used. The animals were starved 24 hours, given a preanesthetic of morphine and atropine, and prepared for aseptic surgery under general ether anesthesia. Each of the animals was subjected to the intraperitoneal implantation of 100 grams of adult dog liver incubated 72 hours and sterilized by autoclaving. The liver material was injected intraperitoneally through a 15 gauge needle pushed through a cautery burn in the abdominal wall. Blood analyses were done on the animals before the liver was injected and repeated some hours later when the animals were at the point of death. The methods used were the same as described in a previous publication.<sup>7</sup> At the time the terminal samples of blood were drawn, 10 c.c. samples of peritoneal exudate were removed for bacteriologic smears and cultures.

All the animals died within 18 hours from the time the liver was introduced. Samples of blood and peritoneal exudate were obtained from 8 of the dogs at the time of, or just before, death occurred. A careful study of smears stained by Gram's method made of peritoneal

exudate showed the presence of occasional gram-negative bacteria with hazy outlines which we believe were killed bacteria introduced with the incubated liver. Only one culture of the eight samples of peritoneal exudate was positive, and we are convinced that most of these animals died with a sterile peritoneal cavity. The changes in the blood were consistent and surprisingly uniform. The results are illustrated by including a typical protocol and table.

#### PROTOCOL DOG 218

3/27/36

A white, well-nourished, female collie. The animal was starved 24 hours and weighed 31 pounds (14.1 kilos.).

8:30 P.M.—Animal given  $\frac{1}{4}$  gr. morphine sulphate and  $\frac{1}{150}$  gr. atropine sulphate.

9:20 P.M.—Given general ether anesthesia and prepared for aseptic surgery.

9:30 P.M.—40 c.c. of blood were removed from the jugular vein for physical and chemical analyses.

9:35 P.M.—100 gm. of dog liver, incubated 72 hours and sterilized by autoclaving, were injected intraperitoneally through a cautery burn in the abdominal wall.

9:45 P.M.—Animal returned to the kennels and offered water.

3/28/36

11:30 A.M.—The animal was lying on its side in coma. Breathing was slow and labored, the pulse weak and thready, and the extremities were cold.

11:40 A.M.—40 c.c. of blood were removed from the jugular vein for physical and chemical analyses.

11:42 A.M.—The animal expired. The dog survived the injection of liver 14 hours and died 2 minutes after the removal of 40 c.c. of blood. Ten c.c. of peritoneal exudate were removed for bacteriologic smear and culture and the body was immediately autopsied. Bacteriologic studies showed that the peritoneal exudate contained no living bacteria.

*Postmortem Findings.*—The peritoneal cavity contained 300 to 500 c.c. of blood-tinged exudate. The intestines were in marked peristaltic contraction. All the peritoneal surfaces were markedly congested and covered with minute pinpoint hemorrhages. The omentum had caught up the major part of the injected liver material. All peritoneal surfaces were covered with a thin, fibrinous exudate. The gallbladder was distended with bile. The temperature of the peritoneal exudate was 106° F. Upon exploring the gastrointestinal tract there was seen a marked hemorrhagic enteritis extending throughout the small bowel, most marked in the duodenum and ileum. There was marked gastritis confined to the fundic portion of the stomach. Upon exploring the thorax the heart was found to be contracted. The lungs were pink with congestion and bled freely from the cut surface.

Immediately after the animals are injected with this preparation of liver they manifest symptoms indicating a severe stimulation of the sympathetic autonomic nervous system. Their pupils are widely dilated; the hair on the back is elevated; the heart rate is profoundly increased and the pulse full and bounding. In several instances, heart arrhythmias and block were observed. This condition lasts for

an hour or more. These animals are very ill and respirations are frequently of the Cheyne-Stokes type. The condition of the animals improves, and 6 to 8 hours following the liver injection they are able to walk about the room. However, they are very weak; the veins are collapsed; and they have a weak and thready pulse. The animals usually pass bloody mucus from the bowel. Their subsequent course is progressively downward. They present all the clinical signs of shock to a marked degree. The physical and chemical changes in the blood of these animals are clearly illustrated in Table VI. There is a marked concentration of the blood associated with a decrease in plasma volume. The blood sugar and CO<sub>2</sub> capacity of the blood plasma are likewise markedly lowered. There is a profound increase in the total nonprotein nitrogen and urea nitrogen of the blood. The

TABLE VI

THE PHYSICAL AND CHEMICAL CHANGES IN THE BLOOD OF DOG 218. THIS ANIMAL WAS INJECTED INTRAPERITONEALLY WITH 100 GM. OF GROUND, ADULT, DOG LIVER, INCUBATED 3 DAYS, AND STERILIZED BY AUTOCLAVING

BLOOD STUDIES	NORMAL	AT DEATH—14 HR.
R.B.C.	8,100,000	12,820,000
W.B.C.	6,850	10,050
Coagulation time	3' 45"	2 min.
Hemoglobin—gm. per 100 c.c.	16	21
CO <sub>2</sub> vol. %	60	27
Hematocrit—% cells	53	77.6
Per cent plasma	47	24.4
Plasma volume in c.c.	803	328
Blood volume in c.c.	1,710	1,370
Blood sugar—mg. per 100 c.c.	182	67
Total N.P.N.—Mg. per 100 c.c.	35.6	178
Total N. (as protein)—gm. per 100 c.c.	25.9	29.2
Blood chlorides as NaCl—mg. per 100 c.c.	428	388
Urea nitrogen—mg. per 100 c.c.	9.3	45

changes in the blood of these animals are more marked than those seen in dogs subjected to the intraperitoneal implantation of any other preparation of liver we have studied.

The following chart was constructed to contrast the physical and chemical changes in the blood of dogs given lethal preparations of incubated liver sterilized by autoclaving with the changes manifested by dogs given different preparations of unincubated dog liver. The four dogs furnishing the data for this chart presented typical findings and represent observations we have made numerous times.

Dog 274 received 70 gm. of the cellular elements of fresh, raw liver. The animal sterilized the peritoneal cavity and survived.

Dog 279 received 100 gm. of autoclaved, fresh, adult dog liver containing the connective tissue portion. This animal died with a sterile peritoneal cavity following the removal of 40 c.c. of blood necessary for complete chemical analyses.



exudate showed the presence of occasional gram-negative bacteria with hazy outlines which we believe were killed bacteria introduced with the incubated liver. Only one culture of the eight samples of peritoneal exudate was positive, and we are convinced that most of these animals died with a sterile peritoneal cavity. The changes in the blood were consistent and surprisingly uniform. The results are illustrated by including a typical protocol and table.

#### PROTOCOL DOG 218

3/27/36

A white, well-nourished, female collie. The animal was starved 24 hours and weighed 31 pounds (14.1 kilos.).

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9:35 P.M.—100 gm. of dog liver, incubated 72 hours and sterilized by autoclaving, were injected intraperitoneally through a cautery burn in the abdominal wall.

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3/28/36

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Immediately after the animals are injected with this preparation of liver they manifest symptoms indicating a severe stimulation of the sympathetic autonomic nervous system. Their pupils are widely dilated; the hair on the back is elevated; the heart rate is profoundly increased and the pulse full and bounding. In several instances, heart arrhythmias and block were observed. This condition lasts for

that these animals die with a sterile peritoneal cavity. Furthermore, autoclaving the liver must certainly have destroyed heat labile bacterial exotoxins. It is apparent, therefore, that heat stable, toxic factors are produced by the process of incubation. This represents the rapid digestion of liver, both by the action of dog liver bacteria and by enzymes present in the liver substance. They could conceivably arise either from the bacterial bodies as endotoxins or from byproducts of liver digestion. Finally, the rapid death of the animals may have resulted in part because of the irritating action of incubated liver on peritoneal surfaces, causing congestion and loss of fluids intraperitoneally. Our next experiment was undertaken to ascertain

TABLE VII

THE PHYSICAL AND CHEMICAL CHANGES IN THE BLOOD OF DOGS SUBJECTED TO INTRAPERITONEAL INJECTION OF 100 GM. OF INCUBATED DOG LIVER STERILIZED BY AUTOCLAVING, AND SUBSEQUENTLY TREATED BY INTRAVENOUS ADMINISTRATIONS OF HARTMAN'S SOLUTION AND 5 PER CENT GLUCOSE

*BLOOD STUDIES	DOG 227—SURVIVED 17 HR.		DOG 226—SURVIVED 12 HR.	
	NORMAL	AT 12 HR.	NORMAL	AT 12 HR.
R.B.C.	8,670,000	9,770,000	8,670,000	11,900,000
W.B.C.	8,750	19,350	17,600	11,450
Coagulation time	2 min.	1' 30"	4 min.	45"
Hemoglobin—gm. per 100 c.c.	11	16	13.5	19
CO <sub>2</sub> vol. %	45	35	50	31
Hematocrit—% cells	49	60	55	81.5
Per cent plasma	51	40	45	18.5
Plasma volume in c.c.	830	252	980	245
Blood volume in c.c.	1,620	630	2,120	1,325
Blood sugar—mg. per 100 c.c.	125	82	169	136
Total N.P.N.—mg. per 100 c.c.	27.6	53	30	54
Total N. (as protein)—gm. per 100 c.c.	21.2	24.3	22	27
Blood chlorides—mg. per 100 c.c.	380	395	390	380
Urea nitrogen—mg. per 100 c.c.	8.3	14.8	8	20

\*The terminal samples of blood were removed 12 hours after the injection of liver and 3 hours after the administration of 1,500 c.c. Hartman's solution and 5% glucose. Dog 226 died following the removal of 40 c.c. of blood. The other animal was given an additional 500 c.c. Hartman's solution and 5% glucose and died 5 hours later.

whether the lives of animals subjected to lethal preparations of incubated liver sterilized by autoclaving could be prolonged by accepted methods of shock therapy.

*Experiment 7.*—Four dogs were injected intraperitoneally with 100 gm. of sterile autoclaved preparations of incubated liver in the same manner as described in Experiment 6. The animals were given intravenous administrations of 500 c.c. Hartman's solution and 5 per cent glucose every 3 hours following the injection of liver until each had received 1,500 c.c. of fluid. The animals revived remarkably with each intravenous medication. From a prostrated stuporous condition they were immediately able to stand on their feet and walk about. However, the improvement was only temporary. Within 3 hours following the administration of fluids the animals were again prostrated

Dog 294 received 100 gm. of raw, fresh liver containing the connective tissue portion. The dog survived 11½ hours and died with bacterial growth in the peritoneal cavity.

Dog 218 received 100 gm. of ground dog liver, incubated 3 days, and sterilized by autoclaving. The dog survived 14 hours and died with a sterile peritoneal cavity.

Chart I indicates that the blood changes are very marked in those animals receiving lethal preparations of fresh, raw liver. They are even more severe in animals receiving preparations of liver which

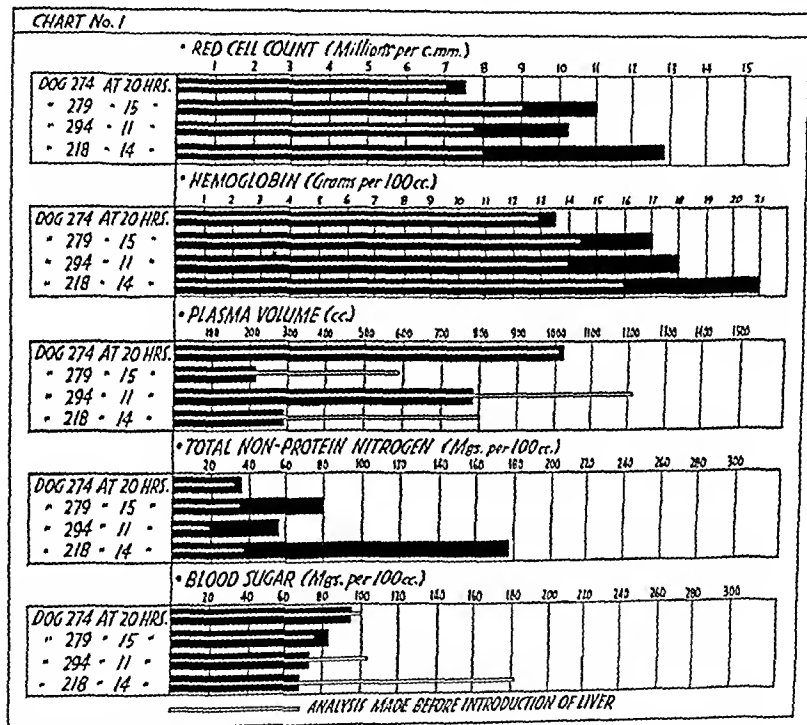


Chart I.—The physical and chemical changes in the blood of dogs subjected to intraperitoneal implantation of various preparations of adult dog liver.

were incubated and sterilized by autoclaving. It is a point of considerable interest that autoclaved fresh liver causes a condition of severe shock. Nevertheless, these animals survive the shock unless large samples of blood are removed during the course of the experiment. Furthermore, our experience shows that complete recovery occurs unless there is an associated bacterial peritonitis. The chart also demonstrates the relative lack of toxicity of preparations from which liver connective tissues have been removed. (See dog 274.)

We wish to emphasize the severe shock and rapid death caused by incubated, autoclaved liver preparations. We have demonstrated

doses (15 gm. per kilo. in one instance) will survive this profound shock, provided the peritoneum remains sterile and provided large samples of blood are not removed during the course of the experiment. Histologic examination of the tissues of these animals shows toxic degenerative changes in parenchymatous organs. We interpret this as evidence that the absorption of liver per se is toxic; but since the animals recover, we do not believe that these toxins are responsible for the rapid death of dogs subjected to intraperitoneal implantation of raw adult dog liver.

Dvorak<sup>4</sup> reported that when dog liver is incubated, a Berkefeld filtrate of the material is fatal when given intravenously to the experimental animal, an observation which might indicate that death was due to bacterial exotoxins formed in the process of incubation. We have repeated Dvorak's experiments and have confirmed his results. However, we observed also that when Berkefeld filtrates were autoclaved and placed intraperitoneally they were equally as toxic as when unautoclaved.

We have repeatedly shown that when fresh, raw liver is incubated and then sterilized by autoclaving it causes rapid death when placed intraperitoneally. The dogs die with profound shock even though the peritoneum remains sterile. We have thus demonstrated that when incubated, autoclaved liver preparations are placed intraperitoneally, death does occur as a result of heat stable toxic substances produced by the incubation of liver; and we are not in sympathy with the concept that death necessarily occurs because of heat labile exotoxins produced by dog liver bacteria. Our experiments demonstrate that rapid death occurs because of toxic substances produced by the action of bacteria upon fresh, raw liver.

Rapid death does not occur when these same bacteria act upon autoclaved, fresh liver in the peritoneal cavity. Dogs which receive autoclaved liver inoculated with living cultures of dog liver bacteria can live for several days with bacteria growing in the peritoneal cavity. Although the dogs eventually die, their death is not the same as that of animals given fresh, raw liver.

We have investigated the nature of the toxins produced by the incubation of dog liver in vitro. We believe that these toxic substances are merely the protein split products of liver digestion in the presence of putrefactive bacteria, namely, peptones, proteoses, and putrefactive amines. Pharmacologically, we have demonstrated the presence of tyramine, histamine-like substances, and various others. The details of this study are being reported in another publication. We further believe that all these toxic substances are rapidly produced by the action of dog liver bacteria upon the autolyzing liver substance either in vivo or in vitro and are probably the toxins responsible for the rapid death of dogs subjected to liver peritonitis.

and moribund. None of the dogs survived more than 18 hours. Smears and cultures taken of peritoneal exudate removed from each of the animals, near or at the time of death, were negative. Blood studies were done on two of the dogs before the liver was injected and repeated later as they were dying. The results of these studies are given in Table VII.

The experiment demonstrates that animals injected intraperitoneally with sterile preparations of incubated dog liver die in irreversible shock from which they cannot be saved by intravenous administration of Hartman's solution and 5 per cent glucose. Postmortem examination revealed findings identical to those observed in dogs dying without the administration of intravenous fluids with the exception that the abdominal cavity of these animals contained 1,500 to 2,000 c.c. of blood-tinged exudate. Table VII shows that the changes in the blood are not appreciably altered by the administration of intravenous fluids. The fluids were not retained by the blood stream and passed rapidly into the peritoneal cavity. It is apparent that following the intraperitoneal injection of sterile incubated dog liver the experimental animal rapidly loses the ability of maintaining any fluid balance and dies in irreversible shock.

#### DISCUSSION AND SUMMARY

The experiments reported in this paper demonstrate the complexity of factors which operate in causing death of the experimental animal subjected to intraperitoneal implantation of liver. We have shown that our experimental results have varied widely according to the character of the liver substance used; whether or not bacteria were present, whether or not we removed the connective tissue from the liver preparations, whether or not the liver was incubated or autoclaved. We have also shown that the peritoneal resistance of the dog has a bearing upon the ability of the animal to survive the intraperitoneal implantation of a given preparation of liver. We have observed that death occurs only when the dog is subjected to liver containing bacteria, or to liver substance upon which the bacteria have been allowed to act *in vitro*. We believe, therefore, that bacteria which normally inhabit the adult dog's liver are responsible for the rapid death of these animals. We have shown, however, that relatively large quantities of fresh liver containing these bacteria may be placed in the peritoneal cavity of the dog without causing death, providing the connective tissues are removed. Under these conditions the dog is able to render the peritoneum sterile.

Our studies on the physical and chemical changes in the blood have shown that a critical state of shock occurs following the intraperitoneal implantation of a sufficient quantity of any preparation of liver. However, dogs receiving fresh, autoclaved liver in massive

doses (15 gm. per kilo. in one instance) will survive this profound shock, provided the peritoneum remains sterile and provided large samples of blood are not removed during the course of the experiment. Histologic examination of the tissues of these animals shows toxic degenerative changes in parenchymatous organs. We interpret this as evidence that the absorption of liver per se is toxic; but since the animals recover, we do not believe that these toxins are responsible for the rapid death of dogs subjected to intraperitoneal implantation of raw adult dog liver.

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We have repeatedly shown that when fresh, raw liver is incubated and then sterilized by autoclaving it causes rapid death when placed intraperitoneally. The dogs die with profound shock even though the peritoneum remains sterile. We have thus demonstrated that when incubated, autoclaved liver preparations are placed intraperitoneally, death does occur as a result of heat stable toxic substances produced by the incubation of liver; and we are not in sympathy with the concept that death necessarily occurs because of heat labile exotoxins produced by dog liver bacteria. Our experiments demonstrate that rapid death occurs because of toxic substances produced by the action of bacteria upon fresh, raw liver.

Rapid death does not occur when these same bacteria act upon autoclaved, fresh liver in the peritoneal cavity. Dogs which receive autoclaved liver inoculated with living cultures of dog liver bacteria can live for several days with bacteria growing in the peritoneal cavity. Although the dogs eventually die, their death is not the same as that of animals given fresh, raw liver.

We have investigated the nature of the toxins produced by the incubation of dog liver in vitro. We believe that these toxic substances are merely the protein split products of liver digestion in the presence of putrefactive bacteria, namely, peptones, proteoses, and putrefactive amines. Pharmacologically, we have demonstrated the presence of tyramine, histamine-like substances, and various others. The details of this study are being reported in another publication. We further believe that all these toxic substances are rapidly produced by the action of dog liver bacteria upon the autolyzing liver substance either in vivo or in vitro and are probably the toxins responsible for the rapid death of dogs subjected to liver peritonitis.

We have further observed that the intraperitoneal absorption of liver proteins which have undergone no bacterial digestion causes a critical state of shock associated with parenchymatous degeneration of the liver, kidneys, and adrenal glands, and we believe that these factors also contribute to the rapid death of these animals.

We are aware that these studies may seem to have little clinical significance. However, if human livers harbor bacteria, it is conceivable that they may be factors in the toxemias and shock associated with liver necrosis. Furthermore, there is an accumulation of evidence that human muscles, or the deep lymphatic spaces, may at times harbor bacteria. In this event, our experimental observations upon the rôle played by bacteria in causing rapid death in liver peritonitis may offer a possible explanation for the fulminant toxemias associated with shock, which sometimes occur immediately following traumatic surgical procedures in human subjects.

We wish to express our appreciation to Dr. W. D. Gatch, under whose supervision our investigations originated. Dr. Lynn Arbogast and Dr. Ralph Gettlefinger rendered valuable technical assistance.

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## RELATION OF DUODENAL REGURGITATION TO THE DEVELOPMENT OF JEJUNAL ULCERS.

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THIS paper is confined to a consideration of postoperative jejunal ulcer; no consideration will be given to the rare primary jejunal ulcer which is probably of different pathogenesis. The terms postoperative jejunal ulcer and gastrojejunal ulcer seem preferable to the term marginal ulcer, because many of the ulcers are opposite the gastrojejunostomy stoma and do not actually extend to the line of the junction of the gastric and jejunal mucosa. Moreover, some of the large jejunal ulcers which do extend to the line of anastomosis possibly originate a short distance away. In this paper, the term duodenal regurgitation refers to any drainage of duodenal contents back into the stomach; the term is not restricted to reflux through the pylorus.

During the past fifteen years much experimental work has been done on peptic ulcer, and most of this work has been on dogs. Apparently, spontaneous chronic gastric and duodenal ulcers occur but rarely in dogs. Acute ulcerations occur with moderate frequency, but these lesions differ in many ways from the usual type of peptic ulcer seen in man, and investigation of these is of little benefit in helping to discover the etiology of chronic peptic ulcer. It might be mentioned, however, that acute infections induced in animals under some circumstances produce acute ulceration of the stomach or duodenum, especially the latter, and sometimes with perforation. Similarly in man, one occasionally sees an acute ulceration with perforation of the duodenum at autopsy in a patient with a fulminating infection or brain lesion. With few exceptions, workers have been unable to produce chronic peptic ulcers in the stomach and duodenum of the dog. Gastric ulcers have been occasionally produced by preventing the regurgitation of duodenal contents into the stomach with simultaneous feeding of hydrochloric acid. One of the few methods by which chronic ulcers resembling peptic ulcers in man can be produced with regularity involves the principle of having gastric juice come in contact with jejunal mucosa unprotected by alkaline duodenal contents. This is the so-called surgical duodenal drainage, familiarly known as the Mann-Williamson<sup>1</sup> operation (Fig. 1). In this operation the pylorus is severed and the duodenal end inverted,



The jejunum is severed just beyond the duodenojejunal junction, and the proximal cut end of jejunum is anastomosed to the ileum while the distal cut end of jejunum is anastomosed to the pyloric end of the stomach. By this means, all the duodenal contents are shunted into the lower ileum, and the gastric juice is emptied into a jejunum which can receive no duodenal contents. After this operation, ulcers form in the jejunum close to the gastrojejunosomy stoma. It has been shown by a large number of workers that this procedure is a most reliable way of consistently producing ulcers which are similar to chronic peptic ulcers in man; whereas, these experimentally produced ulcers are very similar to gastrojejunal ulcers in man, there are important points of difference from gastric and duodenal ulcers. Therefore, it is questionable to what extent results obtained from the investigation of these ex-

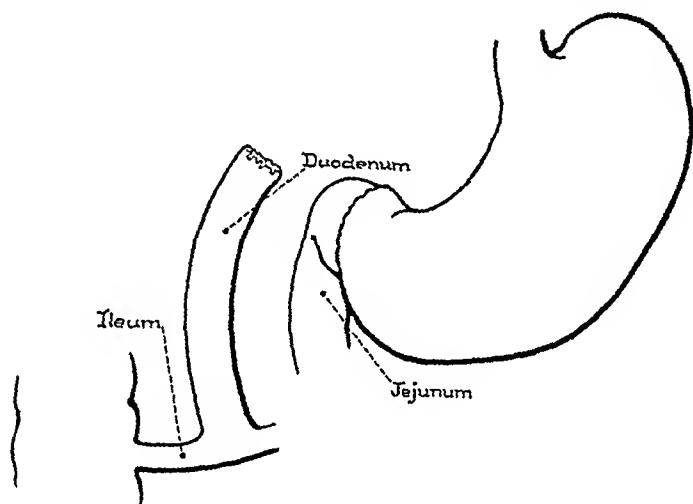


Fig. 1.—Surgical duodenal drainage into the lower ileum (Mann-Williamson operation).

perimental ulcers may be applied to the question of etiology of gastric and duodenal ulcers in man; however, there is much similarity between these ulcers and gastrojejunal ulcers.

Experimentation up to the present time indicates that one of the important etiologic factors in the production of peptic ulcers, and especially of gastrojejunal ulcers, is the action of the gastric juices. The question of whether the acid itself is the main factor or whether the pepsin in the gastric juice is also an important factor, cannot be regarded as settled at the present time. There is rather convincing evidence, however, that other factors, such as muscle spasm, stenosis, mechanical trauma, and nervous reflexes associated with hyperacidity, play an important part. In addition to this, and especially in the consideration of gastrojejunal ulcers, the increasing vulnerability of the intestinal mu-

cosa to gastric juice as the distance from the pylorus increases must be borne in mind. This fact has been convincingly shown by the experimental work of McMaster<sup>2</sup> and others. Those cases in humans where by mistake gastroileostomy was performed instead of gastrojejunostomy, with the rapid subsequent development of an ulcer are further evidence of this fact. Therefore, one principle which must be borne in mind in performing an operation for peptic ulcer is that, other things being equal, the more distal the loop of jejunum which is used for the gastrojejunostomy, the more likely jejunal ulceration is to occur. This is especially important to consider where complicated secondary operations may be required for jejunal ulceration.

In the various surgical procedures used in the treatment of peptic ulcer, there are several objectives which are sought after; and their attainment is considered as increasing the likelihood that the surgical procedure will give a good end-result. The principle objectives are (1) reduction of the acidity, and (2) rapid emptying of the stomach. In speaking of the effect that a particular type of surgical operation has on the acidity, one must be careful to be specific as to what is meant. One usually analyzes the gastric contents and refers to these values. However, in considering the question of acidity in relation to the etiology of gastrojejunal ulcer formation one must remember that a reduction in gastric acidity does not mean a corresponding change in the reaction of the jejunal contents near the gastrojejunal stoma. The pH of the contents in the efferent loop of a gastroenterostomy is the net result of the pH of the gastric contents discharged through the gastroenterostomy stoma and the pH of the jejunal contents itself. In the Mann-Williamson type of surgical duodenal drainage which has been widely used experimentally to produce jejunal ulcers, the important fact is not the acidity of the gastric contents itself, but the absence of alkaline juices on the jejunal side of the anastomosis, except for the slight jejunal secretion. As a result, no appreciable further neutralization of the gastric contents occurs in the upper jejunum. Although by this operation the gastric acidity is somewhat elevated, the change is not as marked as one might think. Examination of the jejunal contents, however, shows a considerable change to the acid side postoperatively.<sup>3</sup> The same principle applies, to some extent at least, to the various surgical procedures used in the treatment of gastric and duodenal ulcer. In a Polya type of resection, for instance, if most of the duodenal contents coming up the afferent loop go back through the gastrojejunostomy stoma into the resected stomach and mix with the gastric contents, the analysis of the gastric contents may show a low acidity; but this acidity may be almost the same as that in the efferent limb of the gastrojejunostomy, since in this instance there is little alkaline juice which is being shunted directly from the afferent to efferent loop of the gastrojejunostomy. In another

case of Polya resection, because of a different mechanical arrangement, a smaller percentage of the duodenal juices passing along the afferent loop might be shunted back into the stomach, and although the gastric acidity itself might be higher than in our previous case, the contents of the efferent jejunal loop actually might be more alkaline. So one must bear in mind that analysis of the gastric acidity does not indicate the pH of the contents of the efferent loop where jejunal ulcers are likely to form.

There has been considerable difference of opinion concerning the relative importance of the reflux of duodenal contents into the stomach in reducing gastric acidity. By some it is considered the chief mechanism by which the gastric acidity is reduced in the later stages of digestion of a meal in the stomach; whereas, others believe its importance is greatly exaggerated. Furthermore, it must be remembered that some constituents of the duodenal contents are a slight stimulus to gastric secretion. However, there can be no doubt whatsoever concerning the importance of the duodenal contents in neutralizing and diluting the gastric chyme after it leaves the stomach. In the case of some of the operations used in the treatment of peptic ulcer, the regurgitation of the alkaline intestinal contents into the stomach is regarded as one of the important points to be achieved; in gastroenterostomy, for example. Furthermore, there is much evidence that considerable reflux does occur.<sup>4</sup> In partial gastrectomy the emphasis is more on the reduction of the acid secretion of the stomach and the rapid drainage of gastric contents than on regurgitation of duodenal secretions.

Since duodenal regurgitation is considered desirable, it is quite surprising to note that McCann<sup>5</sup> reports the development of jejunal ulcers in approximately 80 per cent of twenty-six dogs with gastrointestinal anastomoses through which there was complete regurgitation of duodenal contents into the fundus of the stomach. In fact, he came to the conclusion that jejunal ulcers could be produced as readily by diverting the duodenal contents into the stomach as by draining them into the lower ileum. Furthermore, he did preoperative and postoperative gastric analyses using a test meal and thought that the type of acidity curve was similar. Examination of these curves, however, shows that in the dogs in which the duodenal contents were diverted into the lower ileum, the acidity remained at a high level for a longer time postoperatively. On the other hand, in the cases in which the duodenal contents were drained back into the stomach, there was a slightly lower acidity than in the preoperative analyses.

As far as we have been able to ascertain, this work of McCann has not been repeated by other investigators. However, an arrangement similar to McCann's, with the exception that the duodenal contents were shunted

into the prepyloric portion of the stomach instead of the fundus, has been used in experimentation by at least three workers.<sup>6, 7, 8</sup> They used a total of thirty-seven dogs and obtained only two jejunal ulcers. The question naturally arises whether this difference in the site of the entrance of the duodenal contents into the stomach, with resultant difference in the thoroughness of mixing of the gastric and duodenal juices, could be responsible for the difference in the results. Therefore, it seemed worth while to repeat McCann's experiments with certain modifications. There are some theoretical and practical considerations of considerable importance that these experimental observations bring to one's mind. If it were true that complete duodenal regurgitation were associated with a high incidence of jejunal ulcer and little change in gastric acidity, it would be of considerable clinical importance, because ordinarily duodenal

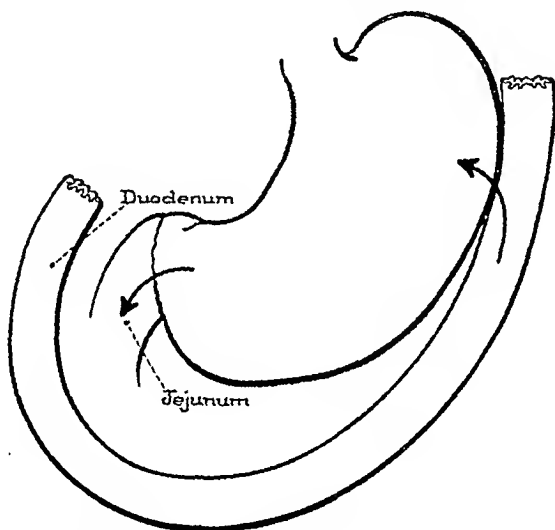


Fig. 2.—Surgical duodenal drainage into the fundus of the stomach.

regurgitation is considered very desirable. In fact, recently there have been proposals of new operations for peptic ulcer based on the principle that the more complete the degree of regurgitation of the duodenal contents, the better the results would be and the less the likelihood of post-operative jejunal ulcer.

#### EXPERIMENTAL DATA

Two groups of experiments were carried out. In one group, a procedure similar to that used by McCann was employed (Fig. 2). Dogs were used as the experimental animals. All operations were performed under ether anesthesia and with the usual aseptic precautions. The abdomen was opened through an upper right rectus incision. The duodenum was severed just beyond the pylorus and the duodenal stump inverted. The jejunum was then divided as short a distance as practical beyond the duodenojejunal junction. The proximal cut end of jejunum was anastomosed to the fundus of the stomach by a side-to-side anastomosis. This was done as far

to the left side of the stomach as was mechanically possible. The distal cut end of the jejunum was anastomosed to the pyloric end of the stomach end-to-end. Before making this anastomosis, the pyloric end of the stomach was cut at an angle; the same was done to the end of the jejunum. This was done in order to obtain a larger stoma and also to eliminate to some extent the sphincteric action of the pyloric muscle so that gastric emptying would not be interfered with. No appreciable portion of the stomach was removed, however. Absorbable suture material was used for all anastomoses. After the immediate postoperative period, the animals were fed on the usual kennel diet.

The animals were permitted to live until they were moribund or died. Seven dogs survived the operation from one and one-half to seven months; most of them lived over six months. In addition, several dogs died within a month of operation; none of these had jejunal ulcers. All the dogs showed progressive loss of weight and strength, in spite of the fact that their appetites were good. Their stools were large and often foul smelling; this was considered to be due to a partial inability to utilize the ingested food. Vomiting was rare. All of the animals became very anemic. Of the seven dogs which lived sufficiently long to be considered for purposes of the experiment, six died apparently of cachexia due to nutritional disturbance. Part of this nutritional disturbance may be due to the fact that in the case of these animals some of the digestive enzymes, such as trypsin, do not have a medium of the proper pH for optimum action. There were no other findings in these animals at autopsy except congestion of the jejunum. Only one dog had jejunal ulceration. This dog had two rather large jejunal ulcers close to the gastrojejunostomy stoma; one of these, just opposite the stoma, had perforated. This animal was the only one to show some dilatation of the stomach. There were also submucosal petechial hemorrhages in the greater part of the jejunum. None of these seven dogs showed any appreciable degree of duodenal dilatation, but in some of the dogs which died shortly after operation and which are not included in the seven of the above group, definite duodenal dilatation was present. These latter dogs vomited considerably postoperatively. In two instances in which this duodenal dilatation and stasis was marked, it was the only obvious cause of death.

Analysis of the gastric contents after stimulation by the injection of histamine was carried out in the case of several animals both preoperatively and postoperatively. In each instance there was a considerable reduction in acidity after operation. Also, in the case of several of the animals, studies of the ability of the stomach to neutralize acid were made before and after operation. The following procedure was employed: After analysis of the fasting gastric contents, 200 c.c. of tenth normal hydrochloric acid were introduced into the stomach. A 10 c.c. sample was removed immediately after introduction and then at fifteen-minute intervals for one and one-half hours or until no more

specimens could be obtained. A considerable increase in the ability to neutralize acid was noted in all cases after complete duodenal regurgitation had been produced by operation.

A second group of experiments were carried out. In this group, a similar surgical procedure was performed, except that about one-half of the stomach was resected in addition. (Fig. 3.) The pylorus was severed, and the duodenal end inverted. The distal half of the stomach was resected; the jejunum was severed just beyond the duodenojejunal junction, and the proximal cut end of the jejunum implanted into the fundus of the stomach side-to-side. The distal cut end of jejunum was anastomosed to the resected end of the stomach end-to-side. This resulted in complete duodenal regurgitation in a resected stomach.

Five dogs survived this operation from two to five months. All the dogs showed changes similar to those seen in the previous group. At

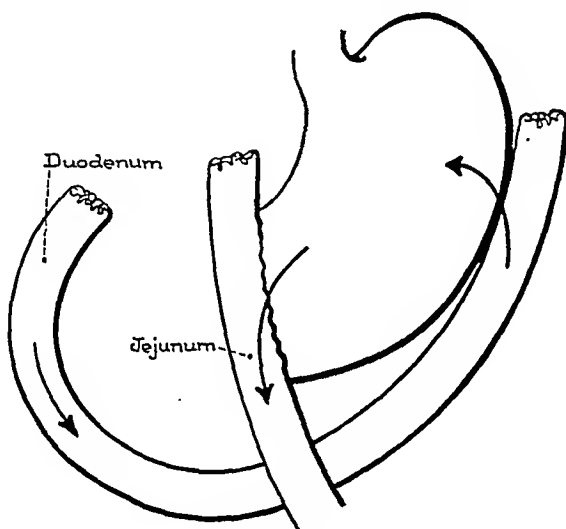


Fig. 3.—Surgical duodenal drainage into the partly resected stomach.

autopsy, only one dog had a jejunal ulcer; this ulcer had perforated. The other dogs died apparently of cachexia from nutritional disturbance.

Gastric analysis in this group showed a somewhat lower acidity post-operatively with histamine stimulation than in the previous group. In one instance only was there anacidity. These animals were able to neutralize acid very rapidly.

#### DISCUSSION

It is not entirely obvious why we obtained such a markedly different incidence of jejunal ulcers from that which McCann reported. It is probably not due to the length of time which the animals survived, because McCann states that most of his dogs developed ulcers within one to three months after operation, while most of our animals survived about six months. If the difference in frequency of jejunal ulceration

were due to the fact that McCann etherized some of the dogs when they refused food and lost weight; whereas, we waited until the dogs died, then probably the ulcers in his dogs were not really chronic in character, although we saw no evidence of scarring of the jejunum at autopsy. The site of entrance of the duodenal contents into the stomach might be a factor, but we implanted the duodenal end of the severed jejunum as far from the pyloric end of the stomach as possible. The size of the gastrojejunostomy stoma at the outlet of the stomach and the fact that we cut the pyloric muscle in such a way as to reduce the sphincteric action of the pylorus might well be the explanation for the difference of our results. Ivy and Fauley<sup>8</sup> and Steinberg and Proffit<sup>9</sup> have shown the great diminution in the incidence of jejunal ulceration in dogs when an anastomosis with a large stoma is made. Furthermore, McCann mentions definite delay in gastric emptying, probably due to stenosis at the gastrojejunostomy stoma; whereas, in our animals gastric emptying was more rapid than before operation. The adequacy of the blood supply in the area where the ulcers form, the types of dogs used, and their diets might all be factors, but cannot be evaluated.

The relationship between the nutritional status of the animal and the development of experimental jejunal ulcers is an important factor to consider. Flood and Mullins<sup>10</sup> recently considered this point and studied the nutritional disturbances in dogs after the Mann-Williamson surgical duodenal drainage. Our dogs showed similar changes, although the changes occurred more gradually. However, a difference in nutritional status does not seem to be the explanation for the difference between our results and those reported by McCann, because our dogs apparently showed the greater evidence of nutritional difficulties, and yet our incidence of ulcer was much less.

Even though we obtained a much lower incidence of jejunal ulceration than McCann reported, one may conclude that in spite of regurgitation of duodenal contents into the stomach with resultant diminution in the acidity of the gastric contents, jejunal ulcers may form, because the jejunum may thereby be exposed to a relatively more acid secretion. This is even true when we have a partial gastrectomy in addition to complete duodenal regurgitation. Apparently there is a mechanism by which the stomach, to some extent at least, controls the acidity of the contents ejected from the stomach. The alkaline duodenal juices to some extent are analogous to added alkaline by mouth, and produce a somewhat similar response of gastric secretion; both cause some secretion of acid but not a sufficient amount to neutralize completely the alkali. However, part of the duodenal alkali is lost, so to speak, as far as being available for neutralization on the distal side of the pylorus. Therefore, the end-result is that the jejunal mucosa is exposed to a more acid contents than if no regurgitation had occurred. To corroborate these points the report of Schmilinsky<sup>11</sup> is interesting. He operated

upon three cases of jejunal ulcer following gastroenterostomy and performed an operation by which there was forced regurgitation of all duodenal contents back into the stomach. One patient died postoperatively; one died one year later of a new perforated jejunal ulcer; while the third had much epigastric distress, a so-called gastritis, and developed dilatation of the duodenal loop. The operation was also carried out on five cases of duodenal ulcer. Several of these had gastrointestinal symptoms of considerable severity after the operation. They also seemed to develop a form of gastritis. An anacidity was not always obtained. Schmilinsky concludes that, whereas, the stomach is physiologically adapted to deal with a small amount of duodenal contents, it is not intended to handle a large amount.

That jejunal ulcers will occur with the same frequency whether all or none of the duodenal contents is shunted back into the stomach, as McCann believed, does not seem to be true. All workers who have used the Mann-Williamson operation report a much higher incidence of jejunal ulcers than we obtained in our experiments. In fact, Owings and Smith<sup>12</sup> report the healing of a certain percentage of jejunal ulcers produced by surgical duodenal drainage when the duodenal contents are later shunted back into the stomach.

#### SUMMARY

In a consideration of the rôle of acidity in the production of jejunal ulcers, the analysis of the gastric contents is a very unreliable guide.

Whereas the more the regurgitation of intestinal contents into the stomach after a gastroenterostomy or gastric resection, the lower the resultant gastric acidity, this regurgitation will not lower the acidity in the efferent loop of the jejunum. Therefore, although the regurgitation lessens the chances of further trouble with the gastric or duodenal ulcer, it does not diminish, but in fact may increase the chances of developing a jejunal ulcer.

Mechanical factors, such as kinks, stenosis, and the muscular spasm, also play a rôle in jejunal ulcer formation.

The details of the mechanical arrangement in each individual case will be an important factor in determining the amount of duodenal contents regurgitated into the stomach after a gastric operation and hence may influence the chances of jejunal ulcer formation.

We have been unable to corroborate McCann's finding of a very high incidence of jejunal ulcer in dogs after drainage of the duodenal contents into the fundus of the stomach. The difference in our results is due probably to the larger gastrojejunostomy stoma which we employed.

Considerable digestive disturbance may result from complete duodenal regurgitation.



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# Editorials

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## The Training of the Surgeon

**B**ARON BOYER'S statement, made early in the nineteenth century, that surgery had reached the greatest heights to which it could ever attain, is another example of how easily the surgical prognosticator may be led astray. The art of surgery and the science upon which it is built are constantly changing and, as a result of this, the preparation of young men interested in a career in surgery must also change.

The training of the barber surgeons was in large part based upon a knowledge of anatomy. It remained for John Hunter to give surgery a firm and lasting foundation in pathologic anatomy. With the development of the aseptic discipline, surgical therapy was revolutionized and in the last quarter of the nineteenth century more was accomplished to place surgery on a firm basis than in all the years which had gone before. It was during this period that symptomatology was correlated with the morbid anatomy of the living patient and not with the end-results of pathologic processes, as observed at the autopsy table.

The art and science of surgery was in large part developing during this period because of the expansion which was taking place primarily in bacteriology, but also in physiology, physiologic chemistry, and pathology. While it was previously considered sufficient for the surgeon to have a background in anatomy and pathology, it has become equally important that he have had a good basic training in these other sciences.

Since the ultimate aim of surgery is to restore function, it is only by the surgeon's ability to do this with increasing effectiveness that we can maintain a dynamic art. To restore function the surgeon must possess an intimate knowledge of normal function, and the methods by which pathologic processes lead to changes in function. Thus, an intimate, working knowledge of what are unfortunately called the pre-clinical sciences is of the greatest importance to the surgical specialist as well as to the general surgeon.

It is training of this type which has resulted in the rapid developments of neurosurgery, thoracic surgery, and the surgery of the cardiovascular system. It is upon the firm foundation of physiology in its broadest aspects that the great advances in the pre- and postoperative treatment of the handicapped patient have been developed.

Many of the ablest minds in the surgical profession have been keen observers. They have, in many instances without knowing it, made a laboratory of the bedside and the operating table, and these can be just as much of a laboratory as the purely experimental workshop.

It has, furthermore, been stated that a rigid discipline in the basic sciences may be necessary for the neophyte who is preparing himself for an academic career in surgery. I cannot see that the training need or should be any different for the surgeon who does not have the opportunity to teach in our medical schools. He will, in all probability, train young men, and as a group the surgical practitioners will be entrusted with a larger number of lives. The surgical practitioner must not only have a working background in the basic sciences, but he must provide himself with the means of keeping in contact with the important advances in these subjects, as they relate to the art and science of surgery.

There are still many surgeons who express their belief that this foundation in the basic medical sciences as a part of the training of the surgeon is overemphasized, with the result that the young surgeon is becoming too scientific; that the ability to use his fingers dexterously is the *sine qua non* of a student's training. A review of the publications of some of these men shows that often they attempt to utilize the developments of the basic sciences to clothe their own contributions, a lack of consistency in the point of view which they take.

It would be folly to state that the technical aspects of surgery had reached their fullest development, but it is, I believe, a just prognostication to state that the improvements in the end-results of surgical therapy will come from an ever enlarging knowledge of the processes involved in maintaining normal function, and our ability to understand the mechanism involved in alteration from the normal.

As long as we refuse to accept this point of view, the training of the surgeon will be distorted, and as Buckle has said, the philosophy of any subject is not at its center but on the periphery where it impinges on all the other sciences.

The training of young men interested in a surgical career should be based upon more than a foundation in anatomy, pathology, and the technical aspects of surgical maneuvers. It should, in part, include training in the other basic sciences. This will bring surgical knowledge from the inner circle to the periphery where the surgeon will meet and interpret the normal and abnormal processes of living tissues, and from such a contact developments cannot help but come.

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### Training the Young Surgeon

THE proper training of the young surgeon is being given a great deal of justified attention, and perhaps the most important recent step is in the formation of the American Board of Surgery for the certification of those properly qualified. In most instances this is going to mean, for the young group, a residency or its equivalent.

In the effort to improve the standard of surgery, a great step forward has been taken. A definite minimum period of hospital training for those who wish to be certified has been established and this, with the hospital standardization of the present and that to come, should insure a favorable circle of better trained men making better institutions and better institutions making better trained men.

We have established standards of premedical education, medical education, hospital training, and we have specified that there must be two years of surgery added to those spent in hospitals (with a fourth year residency). It seems that it would be helpful for those in authority to further aid by providing, as far as possible, positions and work for this young group of well-trained men, thereby aiding them, the hospitals, the surgical dispensaries, and the medical schools.

The American Board of Surgery demands a four-year hospital training and "an additional period of not less than two years of study or practice in surgery." This last regulation is necessarily a more or less loose one, in that a percentage of men will form attachments that are of little value, a marking of time only, while others will obtain positions giving them excellent training and experience. Thus it is seen that, with all the care and thought given, there is, in most cases, a weak link in the chain; namely, the years following a residency or other hospital training. In our present system there is, from graduation on, a step-by-step advance in knowledge and opportunity to the crescendo of the year as resident surgeon when a large experience is obtained; then there is a sharp diminuendo, during which many tangles can be straightened out of the skein, much reading done, notes, records, and ideas clarified and amplified, but the hands are more or less idle.

How to help bridge this gap is a pertinent current question. The need of surgical experience on the part of the young surgeon and the problem of extensive and increasing dispensary and free ward services should be subject to adjustment mutually beneficial. Naturally no hard and fast rules applicable to all hospitals can be established. A large hospital with a five-, six-, or seven-year residency is different from one with a four-year residency. Hospitals affiliated with medical schools are in a somewhat different position from those not so connected, but the discussion of any plan may direct some attention to, and help strengthen, this weak period in the present general scheme until further study crystallizes a more universally acceptable plan.

It may be that the next few decades will see the development of hospitals for postgraduate training different from those now available. (The Roman Catholic Archbishop of Baltimore has at his disposal a fund of \$5,000,000 which he hopes to let grow for an indefinite number of years; and, when it is sufficiently large, he has in mind the establishment of a hospital planned to cover some of the problems outlined above.)

For some years we have had at the hospital\* with which I am connected, a plan that is not without serious faults but which has advantages that may be worth considering. Our hospital, a general one of 250 beds, is connected with the University of Maryland School of Medicine and is used for teaching one-half of the senior class and for some of the junior classwork. The chief surgeon and the staff of attending surgeons, including the specialists, attend the wards and do the teaching. The arrangement of the work of the senior surgeons does not interest us here. The plan for the younger men may perhaps best be traced from below upward. If the resident surgeon is a native of the city or if he decides to remain and desires to become connected with the hospital, he is required to work in the dispensary and do dispensary teaching. If he continues to be earnest, interested and deserving, and if he confines his work to surgery, an effort is made to give him a connection with the ward work. This consists at first of a night service; that is, for one or more nights a week he is on call from 7 P.M. to 7 A.M., to be responsible, with the resident, for the ward cases that come in as emergencies, a senior surgeon being consulted, if necessary. Naturally this gives him a limited type of work, omits, in the main, elective cases, but gives him difficult diagnostic problems, all types of acute conditions, traumatic cases, etc.; but more important, it gives him a connection with, and interest in, the ward work. Further, it puts him in line for promotion. The next older group gets a summer service and looks after the wards between the school sessions. From these two groups the teaching staff is recruited, each regular teacher picking one of the most likely of the younger men as a substitute in case he cannot meet a class. In this way, the younger group is kept interested in the dispensary work, the ward work, and the teaching, at the same time not themselves becoming stagnated. Each substitute has to be prepared to give a clinic or ward class on short notice; he must be ready not only to discuss a case and operate, but he must have dry clinics prepared.

One of the first criticisms will, no doubt, be that this plan interferes with the resident's work. That might be more largely the case in a hospital with five-, six-, or seven-year residency, but it does not hold so true with a four-year man, who is not permitted to do much operating until the latter half of his residency. When he finishes his term, he has seen a great deal and has had a large experience, with from 200 to 300 major operations, but most of his operating comes in the last part of his term.

The residency begins and ends September 1; whereas, the other members of the house staff change July 1. This is done for two chief reasons:

A. Because it allows the outgoing resident the summer months to break in the rotating internes and the assistants, though these latter are usually rotators who have been promoted and know the ropes.

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B. It permits the resident to have two months at the end of his training period when no clinics are being held and during which he gets a large amount of material. It is customary for the young attending man to let the resident do the operating, but he is there, he sees the case, gets the experience, discusses it with the resident, and it is helpful to both and safer for the patient than having the resident unsupervised.

This comes in slight conflict with the rule of the American Board of Surgery requiring "adequate operative experience in which the candidate has assumed the whole responsibility ———." Perhaps there is room here for argument, with the patient having an advocate.

A second objection might be that the supply and demand might not balance. The plan is flexible to a considerable degree. At present we have seven men on night duty—no hardship on any one. The nights could be divided among any less number. For instance, giving three men two nights and the newest recruit one, or giving five men a night each and the sixth two nights, etc.

If appropriate applicants are scarce from one's own ex-residents, outside talent is called upon. If there are too many applicants, it is a survival of the fittest. The attrition of the specialties, increasing private work, indifference, inability to teach, will eliminate a percentage.

A third argument might be that the young attending surgeon does not do the operating. His hands are still idle. This is true to a large extent, but he is seeing cases, is in contact with patients, with teaching, ward rounds, etc., and he can, if he so desires, take an occasional case, if the resident is getting an ample number.

This or some similar plan is suggested to help the applicants for certification. At the same time, it may aid in strengthening the ward services, surgical dispensaries, and may help in the development of future teachers.

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# Recent Advances in Surgery

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CONDUCTED BY ALFRED BLALOCK, M.D.

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## RECENT ADVANCES IN SURGERY OF THE THYROID GLAND

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### THE HISTORICAL BACKGROUND

**S**URGERY of the thyroid, unlike certain other types of surgery, was comparatively well advanced toward its present position even at the turn of the century. Though much knowledge has very recently been added to our information concerning the thyroid gland, a student of the history of the subject must experience some misgivings on finding that with the exception of a few important improvements in the present century some surgeons in the last century achieved almost as much in the surgical management of goiter as is being accomplished today. In a résumé of the advances which have been made in recent years, it is by no means irrelevant to review in a cursory manner the important steps which brought the surgery of the thyroid to the commendable position it already occupied at the beginning of the century.

Desault<sup>1</sup> is accredited with being the first to successfully remove a goiter, an operation which he performed in 1792. At that time rarely were attempts made to operate for goiter. Its surgical extirpation was considered practically impossible. A few sporadic reports were made of such operations. One of the most remarkable early achievements was that of Hedenus,<sup>2</sup> who reported in 1821 that he had removed six goiters successfully and stated that he undertook the operations "to show my students what the operator who has courage, determination, composure, perseverance, and patience, and who is equipped with adequate anatomical and surgical knowledge can accomplish even in the severest cases with the bistoury for the good of mankind."

In the years prior to antiseptic surgery, not only hemorrhage but severe cervical cellulitis and mediastinitis were the barriers to the successful performance of this operation. In Billroth's<sup>3</sup> preantiseptic period, he did 20 operations on the thyroid gland. There were 8 deaths, 6 of which were due to infection. As late as 1883, Billroth<sup>4</sup> said: "If we were compelled to cut through the middle of the gland we would

be confronted with quite an uncontrollable hemorrhage." Mikulicz<sup>5</sup> was one of the first to realize the advantages of removal of part of the tissue of each lobe, and found that he could control the hemorrhage even if he cut through the parenchyma of the gland. He devised an operation similar to the one we use today, a bilateral partial resection. In the period immediately following the introduction of antiseptic surgery, Billroth<sup>6</sup> operated upon 48 cases for goiter, with 4 deaths, 8.3 per cent mortality. To Theodore Kocher<sup>7, 8</sup> belongs great credit for perfecting the operation of thyroidectomy and for being the first to do a large number of cases. He used the collar incision,<sup>8</sup> the origin of which is usually ascribed to him, but it was previously recommended by Boeckel.<sup>9</sup> Gley,<sup>10</sup> in 1891, showed that the parathyroid glands were essential to life, and later Vassale and Generali,<sup>11</sup> in 1895, studied the function of the parathyroids and showed their relation to tetany. According to Dubois,<sup>12</sup> Frederic Müller was the first to show that the metabolic rate was increased in hyperthyroidism. Magnus-Levy,<sup>13</sup> in 1895, demonstrated an increase in oxygen consumption in Basedow's disease, and showed that it returned to normal after recovery from thyroidectomy.

Murray,<sup>14</sup> 1892, was the first to use thyroid extract in the treatment of myxedema.

In 1897, Theodore Kocher<sup>8</sup> reported 1,250 thyroidectomies, and in the last 175 cases had no deaths. Thus, at the beginning of the century, though little was known of the physiology of the thyroid gland, some men, notable among whom were Kocher<sup>8</sup> and Halsted,<sup>15</sup> were performing thyroidectomy with success in many cases and with an appreciably low mortality.

#### ETIOLOGY

The etiology of goiter, while still obscure, has been under close investigation by many authors, and the information gained, especially in recent years, is encouraging, so much so that some disclosures appear to be enticingly near the solution of the problem.

It has long been known and felt that iodine or a deficiency of it was in some way closely bound up with the cause of goiter. It has also been appreciated that throughout the world, especially in mountainous regions and glacial belts, goiter is prevalent. The geographical characteristics and location of goiter have been investigated in recent years by de Josselin de Jong,<sup>16</sup> Hellwig,<sup>17, 18</sup> Turton,<sup>19</sup> and Smith.<sup>20, 21</sup> Smith<sup>20, 21</sup> believes that the incidence of goiter is indirectly proportionate to the amount of solar radiation. Bircher<sup>22</sup> and others believe it is due to water supply. Bircher<sup>22</sup> found that when goiterogenic water was passed through a Berkefeld filter it rendered it free of the goiterogenic substance.

According to Hellwig,<sup>18</sup> the idea that excess calcium in the water is responsible for goiter is over a century old. As early as 1912,



Waller<sup>23</sup> advanced the theory that the essential factor in goiter seemed to be hard water supply. Hellwig's<sup>18, 24</sup> experimental evidence showed that rats fed on a diet deficient in iodine did not develop goiter, but if the diet was not only deficient in iodine but high in calcium chlorides goiter did develop. Hibbard<sup>25</sup> and Thompson<sup>26</sup> corroborate this evidence. Warthin<sup>27</sup> believes that in exophthalmic goiter patients have a typical constitution similar to that of status thymicolymphaticus.

Experimental and clinical evidence on the effect of the sympathetic nervous control of the thyroid gland as an etiologic factor in goiter is not convincing. Work has been done in this field by Cannon,<sup>28</sup> Wilson,<sup>29</sup> Marine, Rogoff and Stewart,<sup>30</sup> and Reid and Holman.<sup>31</sup>

Halsted<sup>32, 33</sup> concluded from microscopic studies on thyroid glands of dogs with low grade infections that infection caused hyperplastic changes in the thyroid gland. Cole and Womack<sup>34, 35</sup> found hyperplastic changes in the thyroid gland following infections in other parts of the body. Mahorner<sup>36</sup> performed similar experiments and found evidence to the contrary.

The possible relationship between psychogenic factors and diffuse toxic goiter have in recent years again been acknowledged by Plummer and Mayo,<sup>37</sup> Mittelman,<sup>38</sup> and Geyer.<sup>39</sup>

Licini<sup>40</sup> after extirpation of the pancreas in dogs found an increase of colloid in the vesicles of the thyroid. On the theory that the thyroxine is a compound of tyrosine and iodine and that a deficiency of tyrosine might result from an absence of tryptic digestion due to poor pancreatic function, Davis, Hinton, and Killian,<sup>41</sup> and Hinton, Morton, and Weeks<sup>42</sup> ligated the pancreatic ducts in dogs and found a storage of colloid with an increased amount of iodine in the thyroid.

Marine and Baumann<sup>43</sup> by excision or injury to the adrenal gland of animals found an increase in metabolism, a condition analogous to exophthalmic goiter.<sup>44, 45</sup> Mahorner<sup>36</sup> failed to find histologic changes in the thyroid gland of dogs under similar experimental conditions. Other evidences of the relationship between the suprarenal and thyroid glands, though not entirely consistent, are the reports by Shapiro and Marine<sup>46</sup> and Tsuji<sup>47</sup> that improvements in patients with hyperthyroidism followed the administration of suprarenal gland; and the reports by Crile<sup>48</sup> that symptoms of hyperthyroidism abate after a denervation of the suprarenal gland, and the recent report of Pemberton<sup>49</sup> of an apparent mitigation of postoperative hyperthyroid crises from the administration of suprarenal cortex, sodium chloride, and sodium bicarbonate and sodium citrate.

Marine,<sup>50</sup> as early as 1914, showed that feeding brook trout hog liver and hog heart produced goiter in the fry in four months and concluded that some other factor than depletion of iodine was causative in the production of goiter. The possibility that some extraneous

goiterogenic substance may be responsible for the disease has been definitely demonstrated experimentally by Webster and others.<sup>51-55</sup> The question as to whether irradiation of the cabbage would change its goiterogenic quality was studied by Westra and Hunter.<sup>56</sup> McCarrison<sup>57</sup> found that soya bean and groundnut would produce goiter in rats provided there was a deficiency of vitamins in the diet. Other clinical and experimental work by McCarrison<sup>58-61</sup> has shown that the following factors are operative in the production of goiter: filth, ingestion of contaminated material, unsanitary conditions, vitamin deficiency, and an excess fat or calcium with a deficiency of vitamin A, B, or C.

Spence<sup>62</sup> found that injecting chickens intramuscularly with methyl cyanide, to which they are resistant, resulted in some goiterogenic action when large doses were used. Cole, Womack, and Ellett<sup>63</sup> studied 90 chemical compounds for goiterogenic properties and found that histamine, xanthine, caffeine, theophylline, and theobromine apparently produced in the thyroid definite desquamation, loss of colloid, and beginning hyperplasia. Marine and Rosen<sup>64</sup> likewise produced chronic progressive bilateral exophthalmos in immature rabbits maintained on a diet of alfalfa hay and oats by daily intramuscular injection of methyl cyanide.

In recent years, studies on the influence of hormones of the pituitary gland on the thyroid gland have indicated a most interesting and most promising field of investigation for the possible cause of hyperthyroidism, suggesting very strongly that the fundamental seat of disturbance in a case of toxic diffuse goiter is the anterior lobe of the pituitary gland.

As early as 1911, Simpson and Hunter<sup>65</sup> called attention to the fact that there is evidence of increase in the size of the pituitary in the thyroidectomized animal. Benedict and Homans,<sup>66</sup> in 1911, found a marked fall of total metabolism in the hypophysectomized dog. Almost everyone is familiar with the classical work of Gudernatsch<sup>67</sup> (1914), who described the changes in tadpoles resulting from feeding them thyroid gland. An early metamorphosis was induced. In 1916, Smith<sup>68</sup> and Allen<sup>69</sup> found that in the hypophysectomized tadpole there was atrophy of the thyroid gland and retardation of metamorphosis. In 1920, Allen<sup>70</sup> performed experiments upon tadpoles, extirpating the thyroid or the hypophysis. Absence of the thyroid gland, he found, fully prevented metamorphosis, but transplantation of the anterior pituitary to the hypophysectomized amphibian resulted in a marked acceleration of growth. Smith and Smith,<sup>71</sup> in 1922, found that intraperitoneal injections of fresh anterior lobe substance made changes in the thyroid in previously hypophysectomized tadpoles. The changes were in the nature of a return to normal from an atrophic picture of the thyroid. These investigations were the basis for further research along these lines and numerous investigators<sup>72-124</sup> have almost uni-

formly reported that extracts of the anterior lobe of the pituitary injected into lower animals result in the following changes: (1) increase in the size of the thyroid gland to as much as sixty times the normal weight, as reported by Shockaert;<sup>72</sup> (2) a decrease in the amount of colloid in the thyroid gland; (3) an increase in the size and number of epithelial elements of the thyroid resembling that seen in the histologic picture of exophthalmic goiter; (4) an increase in the basal metabolic rate; (5) a loss of weight in the experimental animal; (6) exophthalmos; (7) decrease in the iodine content of the thyroid gland; (8) increase in the iodine content of the blood; (9) diminished glycogen content of the liver; and (10) early metamorphosis of tadpoles which is absent if the thyroid has been removed. In other words, repeated subcutaneous or intraperitoneal injection of extract of anterior lobe of the pituitary body into lower animals apparently stimulates the thyroid gland to activity, and in the absence of this hormone there is atrophy of the thyroid gland. In its excess, a condition is produced in lower animals which comes closer to being the clinical and pathologic picture of exophthalmic goiter than has ever been produced by any other method. However, one must not conclude definitely that the thyrotropic hormone of the pituitary gland in excess is the cause of hyperthyroidism. The studies are suggestive that such may be an operative cause, but they do not entirely prove that it is the cause in toxic diffuse (exophthalmic) goiter. Repeated injections of anterior pituitary hormone are not accumulative and apparently after a short time the thyroid gland returns to its normal appearance. Collip and Anderson<sup>73, 74</sup> felt that an antihormone developed in the blood, and they obtained an extract from the serum of a horse injected with thyrotropic hormone which inhibited the action of thyrotropic hormone or by itself depressed the metabolic rate of normal animals. Thompson and coworkers<sup>75</sup> found that the thyrotropic principle in the human elevated the basal metabolic rate but produced no change in patients with marked myxedema.

#### IODINE IN ITS RELATION TO THE THYROID GLAND

Kendall,<sup>125</sup> in 1915, isolated the active principle of the thyroid gland containing approximately 60 per cent iodine. He named this principle thyroxin. Harington<sup>126</sup> accurately determined its formula. Harington<sup>127</sup> believes that thyroxin and diiodotyrosine account for all the iodine in the thyroid gland. He thinks that the natural active secretion contains both thyroxin and diiodotyrosine. Abelin<sup>128</sup> found that diiodotyrosine mitigated the effect of thyroxin. Delcourt-Bernard<sup>129</sup> substantiated these findings. However, Lerman and Salter<sup>130</sup> conclude that diiodotyrosine is calorigenically potent so long as it is part of the thyroglobulin molecule, but loses its activity when separated. The relationship of iodine and iodine content of the gland to

its histology has been studied by Marine and Lenhart,<sup>131</sup> Mosser,<sup>132</sup> Jordi,<sup>133</sup> Rienhoff,<sup>134</sup> Curtis,<sup>135</sup> and others. Plummer<sup>136</sup> introduced the routine use of iodine as a preparation for operation in the exophthalmic goiter patient in 1922, and by this measure the mortality was tremendously reduced.<sup>137</sup> Many studies<sup>138-148</sup> continued to be made on the clinical effects of the administration of iodine to the thyrotoxic patient. The summary of studies in recent years concerning this problem is that in the diffuse toxic goiter (exophthalmic goiter), there is a sharp improvement on the administration of iodine, and that eventually the gland becomes refractory to the administration of iodine and no further improvement occurs. Many authors, including such experimentalists and clinicians as Marine<sup>45</sup> and Means,<sup>149</sup> continue to reiterate the fact that the administration of iodine to the toxic goiter patient as a therapeutic measure other than for preoperative preparation is wrong and does not give the patient the best chance of recovery, which he would have with surgery following preliminary iodine medication.

The determination of iodine in the blood is a long and difficult chemical problem (Aitken<sup>150</sup> and Perkin<sup>151</sup>). It has been found by several investigators that the blood iodine in the thyrotoxic patient is appreciably increased as a general rule. Lahey<sup>152</sup> believes that the determination of the blood iodine has some value in indicating the risk in operation in thyrotoxic patients. It was found that in 70 per cent of patients having blood iodines which were elevated preoperatively, multiple stage operations were performed in 17.9 per cent, while of 30 per cent of patients having hyperthyroidism with normal blood iodine preoperatively, multiple stage procedures were performed in 45.8 per cent, therefore disclosing the possibility that low blood iodine with thyrotoxicosis is indication of a severe grade of hyperthyroidism and one in which multiple stage procedures must be considered as offering the patients the best chance of recovery. Watson<sup>153</sup> described an iodine tolerance test whereby the relative rate of disappearance from the blood stream of intravenously injected iodine may be expressed. The observation suggested that the iodine tolerance test may be a means of providing evidence of diagnostic importance in cases of doubtful thyroid disease.

#### TESTS

The determination of the basal metabolic rate has been the most reliable and most constantly used test for estimating the activity of the thyroid gland, and the degree of severity of the hyperthyroidism.<sup>154-156</sup> However, because the basal metabolic rate is not always a true index of the risk of operating upon a patient with hyperthyroidism, new methods of estimating the severity of the disease and the risk involved have been sought. One method is the determination of the iodine content of the blood, as mentioned above. Goetsch<sup>157</sup> noted some relationship between the sensitivity to adrenalin and the

severity of the disease. His test, however, and the Kottmann reaction<sup>158</sup> have not been accepted as reliable. Recently, however, Brazier introduced a new test.<sup>159-161</sup> Regarding the body as a dielectric and depending upon the fact that the dielectric loss angle is specific for any material, that is to say, the qualitative measure of this property is independent of the size and shape of the piece of material upon which the measurement is based, Brazier found with a special apparatus for measuring the dielectric loss angle that in thyrotoxicosis the dielectric loss angle or impedance angle was much greater than the standard deviation in the normal. The impedance angle was decreased in myxedema and it was increased by thyroxin, and not by other drugs which were tested. For apparently careful work on this subject, Brazier was awarded the annual award of the American Association for the Study of Goiter. Robertson and Wilson<sup>162</sup> and Horton and coworkers<sup>163</sup> failed to confirm or substantiate Brazier's work.

Clinical estimates together with the basal metabolic rate remain for the present at least the most accurate methods for determining the severity of the disease, the risk involved in an operation, and the condition of the patient. The relationship of cholesterol to the thyroid gland has been studied by Hurzthal and Hunt<sup>164</sup> and by McGee.<sup>165</sup> Although apparently there is some relationship between cholesterol metabolism and the thyroid gland, the findings are not consistent enough and have not been standardized to the extent that the determination of the cholesterol in the blood will estimate the status of thyroid activity. Hurzthal and Hunt<sup>164</sup> found that hyperthyroidism caused a marked drop in blood cholesterol, while hypothyroidism results in a marked increase in the blood cholesterol. McGee<sup>165</sup> failed to find the definite correlation between the metabolic rate and the blood cholesterol.

#### PHYSIOLOGY

Besides physiologic activity of the thyroid gland discussed in other sections of this paper, a general discussion of this subject has been contributed by Marine,<sup>166</sup> Boothby,<sup>167</sup> Richter,<sup>168</sup> and others. More recent expansions of our knowledge of the physiology of the thyroid gland have been contributed by Kosdoba,<sup>169</sup> who found that the thyroid hormone increased the absorbing function of the endothelial system and the resistance of the individual, and by Galli,<sup>170</sup> whose experimental work showed that thyroidectomized animals tolerate a tuberculous infection better than normal animals.

#### ANATOMY

Several investigations have been made on the lymphatic connections of the thyroid gland by Mahorner and others,<sup>171</sup> Chouke and his coworkers,<sup>172</sup> and Rienhoff.<sup>173</sup> Halsted,<sup>174</sup> because of the possibility that hypertrophy of the thymus accounted for some of the symptoms

in exophthalmic goiter, in two cases not only did a lobectomy but removed part of the thymus. His deductions were inconclusive. Briane and Funck-Brentano<sup>175</sup> have recently studied variations in the arteries to the thyroid gland, and careful studies on the recurrent laryngeal nerve have been made by Berlin and Lahey,<sup>176</sup> and Berlin.<sup>177</sup> Berlin found that only 65 per cent of nerves course through the tracheoesophageal sulcus. In the remaining instances, the nerves usually traverse the regional zone or penetrate the thyroid gland itself. Special studies of the effect the enlarged thyroid has upon the trachea have been made by Lahey<sup>178</sup> and Schindler.<sup>179</sup>

New and Childrey<sup>180</sup> have studied vocal cord paralysis. Unilateral paralysis results in fixation of the cord in the medium or cadaveric position. The average duration of symptoms is from ten and one-half months to seventeen months. Paralyzed cords in the cadaveric position usually change from this position to the median line within a few months with return of the voice. If the condition is bilateral, dyspnea develops as the voice improves. Hoover<sup>181</sup> offers something material for the treatment of bilateral adductor paralysis. In seventeen of his eighteen cases the paralysis was related to a thyroid condition and in fourteen it followed the thyroid operation. The only method of treatment which the author found of value was submucous resection of the cords and larynx.

#### PATHOLOGY

Numerous studies on the pathology of the thyroid gland in disease and under experimental conditions may be found in the literature. Among these may be mentioned Marine and Lenhart,<sup>182</sup> Wilson and Kendall,<sup>183</sup> Zechel,<sup>184, 185</sup> Rienhoff,<sup>134</sup> Rice,<sup>186</sup> Hellwig,<sup>187</sup> Markowitz,<sup>188</sup> Roussy and others,<sup>189</sup> Rabinovitch and others,<sup>190</sup> Hertzler,<sup>191</sup> and Keilty.<sup>192</sup> Apparently there is definite relationship between the histologic picture of the thyroid gland and its physiologic activity. In certain nodular goiters this relationship is often difficult to demonstrate. Most observers today consider hyperthyroidism as one continuous disease process and make no distinction except that of the degree of acuteness between the so-called toxic diffuse goiter (exophthalmic) and the toxic nodular goiter. Ever since Plummer<sup>136</sup> differentiated exophthalmic goiter and adenomatous goiter with hyperthyroidism, there has been some controversy as to this question, and it is only settled or rather evaded by adopting the classification which best expresses our present knowledge and which is accepted by the American Association for the Study of Goiter<sup>194</sup> and the Standard Classified Nomenclature of Disease,<sup>195</sup> dividing goiter into nontoxic diffuse, toxic diffuse, nontoxic nodular, and toxic nodular, thus ignoring an attempt toward detailed correlation between the microscopic findings and the activity of the gland.

Special studies on the thymus gland in patients with exophthalmic goiter have been made by Blackford and Freligh<sup>196</sup> and Margolis.<sup>197</sup> Hypertrophy of thymus occurred usually in patients under forty years of age with exophthalmic goiter. Its significance is not entirely understood, but attention has already been called to the fact that Warthin associated it with Graves's constitution.<sup>27, 193</sup> Special studies have been made on the hearts of patients dying with hyperthyroidism by McEachern and Rake.<sup>198</sup> Cardiac hypertrophy was not a constant finding, and it was impossible to ascribe the cardiac phenomena to structural changes in the muscles. These same investigators,<sup>199</sup> recently studying the problem on an experimental animal, found that the administration of thyroxin to animals produced no recognizable changes from the normal in the heart or the tissues studied pathologically. On the other hand, Parenti and Poloni<sup>200</sup> found in rabbits with thyrotoxicosis induced by the administration of thyroid extract an immediate reaction of the muscles to the injection, consisting of serous exudate with cloudy swelling of the fibers and loss of transverse structure of the fibers, or homogenous appearance of the muscles, and an increase in protoplasm, indicating a moderate degeneration of the contractile part of the muscle.

Meyer,<sup>201</sup> studying congenital cysts and fistulas of the neck, reemphasized that to cure thyroglossal duct cyst there must be complete removal of the cyst, a portion of the hyoid bone, and the tissues running from the center of the hyoid bone to the foramen caecum.

Inflammatory lesions of the thyroid gland have been discussed in recent years by Graham and McCullagh,<sup>202</sup> Nestmann,<sup>203</sup> Rankin and Graham,<sup>204</sup> Clute and Lahey,<sup>205</sup> and Boyden and others.<sup>206</sup> Inflammatory lesions have been divided clinically by Clute and Lahey<sup>205</sup> into simply thyroiditis, suppurative thyroiditis, and chronic thyroiditis. The last, being the most common, may be more difficult to diagnose before operation. Myxedema may supervene after the parenchyma has been destroyed in the inflammatory process. Entire removal of isthmus and suture of ribbon muscles to the remaining lobes to prevent reformation of scar over the trachea has been advocated by Lahey.<sup>207</sup> Rankin and Graham,<sup>204</sup> discussing tuberculosis of the thyroid gland, found that it occurred in approximately 0.1 per cent of over 20,000 surgical specimens of the thyroid. The diagnosis was made microscopically. Rienhoff in discussing this paper called attention to the fact that possibly the microscopic appearance of tuberculosis in the thyroid gland is not a true indication of the presence of this disease: that guinea pig inoculations of specimens showing this appearance in his experience failed to demonstrate the tuberculous bacilli.

#### LIVER

Only recently has the frequency and severity of the pathologic changes of the liver in hyperthyroidism been appreciated, and in only

the immediate past has the clinical significance of these lesions been disclosed. For a long time it has been recognized (Habershon,<sup>208</sup> Sutcliffe,<sup>209</sup> Eder,<sup>210</sup> Kohn,<sup>211</sup> Kerr and Rusk,<sup>212</sup> Kerr,<sup>213</sup> Crotti,<sup>214</sup> and Hertzler<sup>191</sup>) that jaundice occasionally occurs with severe hyperthyroidism. Weller,<sup>215</sup> studying the hepatic lesions in groups of autopsies of 44 cases showing thyrotoxicosis, found chronic parenchymatous hepatitis in 50 per cent of the livers. Assmann<sup>216</sup> showed that there was damage to the liver in exophthalmic goiter, the anatomic changes being fatty metamorphosis and in long-standing cases cirrhosis. Lewis<sup>217</sup> in studying 12 livers of patients dying from thyrotoxicosis found one weighing only 960 gm. and attributed it to alcoholic cirrhosis. Beaver and Pemberton<sup>218</sup> in an important study on the pathology of the liver in cases of exophthalmic goiter found on studying 170 cases at necropsy that 23, or 21.5 per cent, showed jaundice. The changes in the liver were divided into acute and chronic, the former being fatty metamorphosis and central and focal necrosis, and the chronic lesions being simple and subacute yellow atrophy or cirrhosis. Acute lesions were present in 91.5 per cent of the cases, and the liver weighed less than the normal in 62.5 per cent. Extremes in weight were 644 gm. and 2,450 gm. They found relationship between the degree of duration of thyrotoxicosis and the severity of liver damage. Mahorner<sup>219</sup> has shown that jaundice in hyperthyroidism due to toxic degeneration disappeared rapidly after the relief of the hyperthyroidism by resection of the thyroid.

The clinical importance of damage to the liver from hyperthyroidism has only slowly been appreciated by clinicians and surgeons. Youmans and Warfield<sup>220</sup> found clinical impairment in 50 per cent of livers tested for liver function by liver function tests. Kuriyama<sup>221</sup> found that the glycogen diminished in the liver in animals fed with thyroid extract. Eitel and Loeser<sup>100</sup> and others found that repeated injection of extract of the anterior lobe of the pituitary resulted in reduction of the glycogen content of the liver, apparently due to the fact that the thyroid was stimulated to a certain degree of hyperactivity. Lahey<sup>152</sup> advanced evidence to show that the severity of hyperthyroidism is in some measure proportionate to hepatic damage and insufficiency. Maes, Boyce, and McFetridge<sup>222</sup> substantiate this and believe the test to be a guide to clinical improvement before operation. Thus, only slowly has been appreciated the significant fact that the liver is damaged in hyperthyroidism, and its present-day practical status, the realization of the necessity for administration of dextrose as in other conditions in which there is liver damage. Probably a number of patients with severe postoperative reaction will not only be greatly benefited, but may be actually saved by the administration of larger quantities of dextrose intravenously.



## MALIGNANT TUMORS OF THE THYROID GLAND

A number of worthy contributions have been made recently to the study of malignancy of the thyroid gland. In reviewing the literature, one is impressed with the total lack of uniformity in terminology and classification of the different types of tumors. The incidence of malignancy of the thyroid gland has been estimated by Graham<sup>223</sup> to be slightly less than 2 per cent of thyroids examined in the laboratory; by Clute and Warren<sup>224</sup> as 2.8 per cent of operated thyroids; by Pemberton<sup>225</sup> as 1.66 per cent of all benign enlargements of the thyroid coming to operation, and by Dinsmore and Crile<sup>226</sup> as present in 1 per cent of all patients subjected to thyroidectomy. This surprisingly high incidence of malignancy of the thyroid in those patients operated upon is justification for urging patients with nodular thyroids to have them removed. Pemberton<sup>225</sup> estimates that in 87 per cent of all cases there was evidence of preexisting benign goiter. Smith, Pool, and Olcott<sup>227</sup> found a preexisting adenoma in 92.6 per cent of the cases of thyroid malignancy. The metastatic lesions of tumors of the thyroid have been studied by Breitner,<sup>228</sup> Sutherland and others,<sup>229</sup> and Copeland.<sup>230</sup> Engelstadt<sup>231</sup> demonstrated that the metastases of carcinoma of the thyroid produced the active secretion of the thyroid gland, thyroxin. Pack and Craver<sup>232</sup> attempted to show by roentgenograms changes in the larynx resulting from thyroid tumors. This method is not to be relied upon for diagnostic accuracy. Mulvihill<sup>233</sup> compared the incidence of malignancy in Berlin with that in New York and believes that the American surgeons operate upon their cases early because they appreciate the indications for operation earlier in this country.

The proper treatment for carcinoma of the thyroid gland is surgery combined with x-ray or radium therapy (Graham,<sup>223</sup> Clute and Warren,<sup>224</sup> Pemberton,<sup>225</sup> Dinsmore,<sup>226</sup> Schreiner and Murphy,<sup>234</sup> Stewart,<sup>235</sup> de Quervain,<sup>236</sup> Dunhill,<sup>237</sup> Clute and Warren,<sup>238</sup> and Bowing<sup>239</sup>). Zuppinger and Rohrer<sup>240</sup> advocate fractional irradiation alone. The prognosis for cancer of the thyroid is not bad if extirpation can be accomplished followed by radiation therapy. Pemberton<sup>225</sup> reported that of 204 cases 32 per cent are living after a lapse of from three to eighteen years, and de Quervain<sup>236</sup> reported 54 per cent living after three years. Crile and Crile<sup>241</sup> in a recent article described a radical operation for malignant tumors of the thyroid gland. They emphasize that approximately 80 per cent of malignant tumors of the thyroid gland are malignant adenomas, and that malignant adenoma and papillary carcinoma are the only types of malignant tumors in their experience which have been cured by surgery. Since these tumors have a tendency to metastasize through the blood vessels, the veins, they describe an operation for excision of the entire lobe of the thyroid with the veins, even the internal jugular, on that side.

Aberrant thyroid glands have a tendency to become malignant. This subject has been discussed by Cattell<sup>242</sup> and Lazarus and Rosenthal.<sup>243</sup> Misplaced thyroid glands apparently develop from the branchial pouches. According to Lazarus and Rosenthal,<sup>243</sup> 70 per cent of the aberrant thyroids give rise to neoplasms of the papillary type. Complete excision results in a favorable prognosis. All cases should receive x-ray therapy postoperatively. Valdoni<sup>244</sup> described a case of malignancy of the thyroid gland in which metastatic lesions were found to extend into the jugular vein and fill it with an adherent tumor. The entire jugular vein together with its tributaries was resected and the patient was examined twenty months after operation with no evidence of recurrence.

#### CLINICAL ASPECTS

Attention has already been called to the controversy which still continues as to whether hyperthyroidism itself may be divided into one or several different types. Hertzler<sup>245</sup> considers all goiters as one disease process, the degree of toxicity being only a stage in the process. This concept is supported by Wendel.<sup>246</sup> Bram,<sup>247</sup> on the other hand, attempts to show the clinical points of difference, differentiating as two distinct entities toxic adenoma and exophthalmic goiter, as did Plummer previously. Fortune<sup>248</sup> again calls attention in recent years to the constitutional evidence of a distinct type that develops Graves's disease and pathologic evidence of Graves's constitution (Warthin<sup>27</sup>) in 90 per cent of the cases. Roeder and Killins<sup>249</sup> call attention to a type of hyperthyroidism in which there is a normal or sub-normal basal metabolic rate with progressive exophthalmos, but with hyperplasia and hypertrophy of the cells of the follicles. Excellent descriptions of the clinical aspects of the disease may be found in many systems and monographs mentioned herein, and recently in a brief but noteworthy contribution by Pemberton and Haines<sup>250</sup> in Christopher's *Textbook of Surgery*. Mahorner<sup>251</sup> discussed the clinical aspects of goiter and called attention again to the characteristic nail changes in toxic goiter, illustrating them with photographs. Hill<sup>252</sup> studied hyperthyroidism with relation to the sex events in the female and found that the onset of toxicity was frequently coincident with one of the major changes, such as puberty, puerperium, or climacteric. Meldolesi<sup>253</sup> found menstrual disturbances in 76 per cent of cases of toxic diffuse (exophthalmic) goiter, which he termed "Flajani-Basedow's disease."<sup>\*</sup> Amenorrhea was more frequent in the severe type of the disease. Studies by Mussey, Plummer, and Boothby<sup>254</sup> and Bothe<sup>255</sup> on the association of hyperthyroidism and pregnancy indicate that there is little doubt that the best prognosis for the mother and child is for the treatment to be directed to the thyroid,

\*Parry described exophthalmic goiter in 1786, Flajani in 1800, Graves in 1835, and Basedow in 1840.

the treatment, especially in the severe type of the disease, being extirpation of the gland. The prognosis is good when this is done. Helmholtz,<sup>256</sup> McGraw,<sup>257</sup> and Cattell<sup>258</sup> have made contributions on the study of thyroid disorders in childhood. According to Cattell,<sup>259</sup> approximately 1 per cent of patients with thyroid disorders are under thirteen years of age. Hyperthyroidism is generally more severe in children, and it should be treated by the same measures as it is in adults. Dunnean<sup>259</sup> has called attention to the fact that both hypothyroid and hyperthyroid states, despite their contrast in clinical picture, are associated with arthritic syndromes. In hyperthyroidism the capsular and periarticular changes, usually in the upper extremity, are similar to those in atrophic polyarthritis. The condition is corrected by surgical resection of the thyroid gland.

Recently attention has been called to the association of exophthalmic goiter with several diseases of the central nervous system. Cohen and King<sup>260</sup> noticed simultaneous occurrence of myasthenia gravis and exophthalmic goiter. Mussio-Fournier<sup>261</sup> reports five cases of familial infantilism due chiefly to hypophyseal insufficiency, but with an associated thyroid insufficiency. The subjects were a brother and four sisters. Thyroid insufficiency was probably secondary to hypopituitarism. Dunlap and Kepler<sup>262</sup> recorded the unusual relationship of exophthalmic goiter with the peculiar syndrome of familial periodic paralysis, in which true paralysis occurs sporadically. In four cases in which they found the association, none of the attacks of paralysis occurred prior to the development of the symptoms of exophthalmic goiter. The plausible explanation appeared that recurrence of attacks of paralysis was an inherited characteristic and the exophthalmic goiter was the precipitating factor. The possibility of goiter's being an hereditary dominant characteristic was present in a family reported by Bing.<sup>263</sup>

A possible relationship between the activity of the thyroid gland and the reticuloendothelial system has been noted above. Pascual and coworkers<sup>264</sup> placed emphasis on the relationship between the thyroid and hemoglobin metabolism, which they say is manifested by the anemia which accompanies myxedema, by the fact that hyperthyroidism may be associated with hyperbilirubinemia, and by the fact that splenomegaly is frequently noted in hyperthyroidism. They noted that the administration of splenic extract in patients with hyperthyroidism resulted in a fall in the basal metabolic rate. Treatment of hyperthyroidism, they declared, decreases the hemoglobin metabolism and lowers the blood pressure. Another conjecture about a relationship between the thyroid gland and the blood is cited by Friedgood<sup>265</sup> who, because lymphatic leucemia is usually associated with an elevation of the basal metabolic rate and because of the depressing effect of iodine on basal metabolism in exophthalmic goiter,

studied the effect of Lugol's solution on the metabolic rate, clinical picture, and laboratory findings in cases of lymphatic leucemia. The administration of Lugol's solution produced a response similar to that seen in exophthalmic goiter. From this the author concludes that exophthalmic goiter is not a disease of the thyroid gland, but primarily a disturbance of the sympathetic nervous system. In some cases of lymphatic leucemia Lugol's solution seems to increase the hemorrhagic tendency and to lower the erythrocyte count and the hemoglobin. There was reduction of nervous manifestations and the size of the lymph nodes and the total leucocyte count. Hubble<sup>266</sup> in reviewing the literature on the influence of the endocrine system in blood disorders found the general impression to be that the thyroid hormone stimulates the formation of erythrocytes and lymphocytes and thus has a tendency to depress granulocytes.

From a clinical study, Golden and Abbott<sup>267</sup> concluded that hyperthyroidism produced an abnormal elimination of calcium. Cohen,<sup>268</sup> because of the association in the same individual of leg ulcers and myxedema and the prompt response of both to thyroid extract, believes that there is a relationship between circumscribed myxedema of the legs and leg ulcers in which there is an obscure etiology.

Certain advances in the knowledge of the relationship between the activity of the thyroid gland and carbohydrate metabolism have been made in recent years. Attention has already been called to the disappearance of glycogen from the liver in the hyperthyroid state. Hatlehol<sup>269</sup> investigated carbohydrate tolerance in hypothyroid and hyperthyroid states and found pronounced disturbances in the hyperthyroid state which were corrected by thyroidectomy. John<sup>270</sup> in an excellent paper on hyperthyroidism and carbohydrate disturbances found that the average incidence of true diabetes in hyperthyroid patients was 2.3 per cent; whereas, the incidence of hyperthyroidism in diabetic patients is 1.68 per cent. After operation for hyperthyroidism, diabetics improved in 55 per cent of the cases, remained stationary in 15, became worse in 30. Recently, Wilder, Foster, and Pemberton<sup>271</sup> found slight improvement following total thyroidectomy for diabetes, but not enough to justify adopting the procedure for routine treatment for severe diabetes. Womack and Cole<sup>272</sup> record two cases showing clinical and pathologic evidence that the thyroid gland tends to undergo compensatory hypertrophy when there is hypoglycemia due to hyperactivity of the islands of Langerhans. Hyperthyroidism masked under the appearance of gastrointestinal symptoms, hypertension, and cardiac disease has been the subject of papers by Verbrycke,<sup>273</sup> Parkinson and Hoyle,<sup>274</sup> and Towers.<sup>275</sup> It has long been known that the predominant symptoms of hyperthyroidism may be cardiac. Only the failure to think of the possibility of the thyroid's being the fundamental cause of a heart condition should ever result in an incomplete diag-

nosis. Excellent discussions of the cardiac features of goiter have been made by Pemberton and Willius<sup>276</sup> and Lahey,<sup>277</sup> both striking a note of hopefulness for this seemingly seriously ill group of patients. Even in the face of complete cardiac decompensation, the result of hyperthyroidism, thyroidectomy will result in a dramatic cure.

To Lahey<sup>278</sup> goes the credit of identifying a type of clinical picture of hyperthyroidism in which the prognosis is extremely grave, though to all appearances the patient may be a safe risk. He calls it apathetic thyroidism. The clinical picture is characterized by an appearance of nonactivity, apathy, hyperthyroidism with relative inactivity. The pulse varies from 100 to 120, and the basal metabolic rate from 20 to 40 with a relatively small thyroid. Lahey<sup>278</sup> warns against too early and too much surgery in these individuals in whom the disease is much more severe than it appears.

Thyroid tissue tumors of the ovary have been discussed recently by Masson and Mueller<sup>279</sup> and Sanders.<sup>280</sup> No less than 80 cases of struma ovarii were found in the literature by Sanders,<sup>280</sup> who reported a large ovarian thyroid tumor.

An excellent review of the subject of lingual thyroid has recently been made by Montgomery.<sup>281</sup> By lingual thyroid the author refers to thyroid tissue occurring at the base of the tongue, rarely in the body of the tongue. There are approximately 144 authentic cases on record. The symptoms are dysphagia and dysphonia, rarely hyperthyroidism. In 75 per cent of the cases the thyroid is absent in the neck. Postoperative hypothyroidism occurred in 70 per cent of cases in which the lingual thyroid was removed. Because of this fact, the author recommends trial medication of desiccated thyroid and iodine, if biopsy discloses no urgent indication for excision.

Oswald<sup>282</sup> and others have called attention to the simultaneous occurrence of myxedema and hyperthyroidism. This paradoxical condition is apparently not rare in postoperative states and is essentially the coexistence of certain features of each condition.

#### EXOPHTHALMOS

Recent investigations have given a more acceptable explanation of the true nature of exophthalmos in toxic diffuse goiter. As early as 1910, Gley<sup>283</sup> reported the spontaneous development of exophthalmos in thyroidectomized animals. Shoekaert<sup>72</sup> was able to produce exophthalmos in ducks by the repeated injections of anterior pituitary hormone. Loeb and Friedman<sup>105</sup> and Friedgood<sup>284</sup> produced exophthalmos in guinea pigs by repeated injection of anterior pituitary hormone. Friedgood<sup>284</sup> confirmed this observation and believed that the ability of the anterior pituitary extract to induce prominence of the eyes is more apparent in the presence of hypothyroidism than in hyperthyroidism. This may in some measure explain certain increases clini-

cally in the degree of exophthalmos after thyroidectomy. Marine and Rosen<sup>285, 64</sup> produced exophthalmos in immature animals by injecting pituitary extract and by injecting cyanide, preferably methyl cyanide, into animals kept on a diet of alfalfa hay and oats. The removal of superior cervical ganglion completely abolished exophthalmos produced in rabbits by cyanide administration, at least during the first two or three months of its existence. Several papers concerning ephedrine and adrenalin in hyperthyroid states have substantiated the experimental observations of Marine and Rosen<sup>285</sup> concerning the sympathetics. Justin-Besançon and coworkers<sup>286</sup> found that of a number of drugs tested, ephedrine was the most likely to produce exophthalmos. Thyroxin alone did not produce the symptoms, but sensitized the animal to the effect of ephedrine and adrenalin and other sympathetic stimulants. Labbe and coworkers<sup>287</sup> found that when thyroxin was given in daily doses of 10 mg. to obese persons, signs of hyperthyroidism developed but no exophthalmos. When, however, 50 mg. of ephedrine were injected ten minutes after the administration of thyroxin, marked exophthalmos resulted within five minutes and persisted for two hours. These observations are further substantiated by Sainton and Hesse,<sup>288</sup> who observed in an obese patient with a low metabolic rate that administration of thyroxin rapidly reduced her weight and raised her metabolism. Finally the patient was placed on thyroxin and 15 drops of adrenalin by mouth. The basal metabolic rate rose to +59 and marked bilateral exophthalmos developed. When the adrenalin was discontinued the exophthalmos disappeared in four days. These striking findings would seem to indicate that exophthalmos is due to sensitization of the sympathetic system to adrenalin by thyroxin. Clinical studies of exophthalmos in recent years have been made by Reudemann,<sup>289</sup> Cattell,<sup>290</sup> and Plummer and Wilder.<sup>291</sup> Plummer and Wilder found that the incidence of association of exophthalmos with diffuse toxic goiter is now only about 40 per cent, as it has decreased in recent years. Plummer and Wilder<sup>291</sup> explain the occurrence of exophthalmos in toxic goiter by spastic contraction of fibers of Müller's muscles which act against weakened extraocular muscles. Indications available indicate that there is little edema and very little venous congestion and that the orbital muscles are small and degenerated. Cattell<sup>290</sup> found that exophthalmos is present in 46 per cent of 860 cases of exophthalmic goiter. Exophthalmos was completely relieved in 50 per cent of the cases operated upon, improved in an additional 13 per cent, not improved in 22 per cent, and in 1 per cent it increased after operation. Zimmerman<sup>292</sup> has considered the group of patients developing exophthalmos after operation.

King<sup>293</sup> postulates that exophthalmos develops because of the accelerated circulation in the orbital cavity, more blood entering than

can be readily evacuated by the vein, resulting in edema and connective tissue formation. Naffziger<sup>294</sup> has devised and successfully used an operation for malignant progressive exophthalmos. Naffziger's operation consists in removing the roof of the orbit for decompression. He found the extraocular muscles greatly increased in size, which increase histologic examination showed to be due to the presence of edema, round cell infiltration, and fibrosis, rather than to a true hypertrophy of the muscles.

#### POSTOPERATIVE PARATHYROID TETANY

After clinical studies on postoperative tetany, Sjostrom<sup>295</sup> called attention to the fact that the condition tends to become latent. Though the patient may be fully capable of working, calcium content of the blood may remain low. The relationship between the thyroid and parathyroid glands has been discussed by Ask-Upmark,<sup>296</sup> who calls attention to the relation of the thyroid to the mineral metabolism as evidenced by the fact that calcium intake as well as iodine deprivation favors the development of goiter. The thyroid exerts an influence upon calcium and phosphorus metabolism. An excellent discussion of tetany with detailed methods of management has been presented by Boothby, Haines, and Pemberton.<sup>297</sup> Calcium and viosterol suffice for the milder forms. Parathormone may be used in the more severe cases. A very significant piece of work has been presented by Stone, Owings, and Gey,<sup>298</sup> who point out the possibilities of transplantations of living grafts of thyroid and parathyroid glands. In order to adapt the graft to the host, they first culture the tissue to be transplanted in an artificial tissue medium containing the body fluids of the recipient. Grafts thus transferred are more likely to survive. In two cases in human beings they were able to relieve the symptoms of parathyroid deficiency by transplanting tissue in this manner. An equally significant presentation is that of Levine,<sup>299</sup> who following an original attempt by Oppel, in 1925, to cure parathyroid tetany by transplantation of a segment of bone so treated a patient who had active postoperative tetany. Convulsions disappeared shortly after the bone transplantation and even before blood calcium was increased. Convulsions had responded only temporarily to injections of calcium, but after implantation of a fragment of bone 6 cm. long, 2 to 3 cm. wide, and from 8 to 10 cm. thick, recovery ensued.

#### TOTAL THYROIDECTOMY

The commendable work of Blumgart and his coworkers<sup>300-304</sup> on the velocity of blood flow was a factor which led to a new treatment for intractable heart disease in individuals with a normal thyroid gland. The work of Blumgart and his associates principally showed that the rate of blood flow was proportionate to the basal metabolic rate. In hyperthyroidism it was increased, in myxedema it was decreased.

Also, in chronic heart disease with decompensation it was decreased. An additional observation made by Levine,<sup>305</sup> that improvement followed subtotal thyroidectomy in a patient suspected of having masked hyperthyroidism but in whom histologic examination proved the gland to be normal, suggested that the extirpation of the normal thyroid might be helpful in cardiac failure not due to thyrotoxicosis. Other studies by Rosenblum and Levine<sup>306</sup> on patients with hyperthyroidism and heart disease led them to conclude that the occurrence of striking improvement following subtotal thyroidectomy in a patient with advanced congestive heart failure in whom the thyroid was normal suggested that this operation on the normal thyroid might be of value in treatment of various forms of cardiac disease. The first cases<sup>306</sup> in which thyroidectomy was deliberately undertaken in patients with congestive heart failure in whom the thyroid gland was clinically normal had only a subtotal thyroidectomy and only a temporary improvement. Surgeons were urged to take out more and more of the gland and eventually total thyroidectomy was done in all instances in which it was desirable to reduce the basal metabolic rate and thereby the velocity of the blood flow to a level commensurate with the abilities of the heart. Numerous other articles<sup>307-322</sup> have been written on the subject, mostly by Blumgart, Levine, Berlin, Cutler, and Eppinger. In a summary of the work by Berlin,<sup>317</sup> he states that approximately 70 per cent of the patients with either angina pectoris or congestive heart failure who were operated upon from one to two and one-half years ago have shown marked to moderate improvement. There was an absence of mortality in the last 62 cases admitted for operation. Most observers agree now that poor results are due to difficulty in selecting cases. Clark, Means, and Sprague<sup>318</sup> outline the following contraindications: (1) cases in which the patient has not been given the benefit of entirely adequate medical treatment over a sufficient period of time to evaluate medical care; (2) cases showing rapid progressive cardiac condition in spite of medical care; (3) cases in which the heart disease is so severe that the patient is unable to establish and maintain compensation on treatment with digitalis and bed rest; (4) cases with high grade mitral stenosis or other mechanical defects giving rise to high venous pressure which is sustained after the restoration of compensation; (5) cases with low preoperative metabolic rate (Berlin and Blumgart<sup>312</sup> state that a B.M.R. of -20 per cent or below is contraindication); (6) cases with severe renal insufficiency; (7) cases with chronic pulmonary disease of any type; (8) cases with malignant or severe hypertension, especially if this is associated with generalized arteriosclerosis; (9) cases with active rheumatic infection, bacterial endocarditis, etc.; (10) cases with recent coronary thrombosis; and (11) cases with status anginosus. There remain certain cases of intractable incapacitating heart disease in which total thyroidectomy is not contraindi-



cated and in which it may be beneficial. Parsons and Purks,<sup>320</sup> collecting information from various sources, summarize the results in a manner that would indicate that the operative mortality from congestive heart failure is approximately 10 per cent, that the results are excellent in approximately 35 per cent of cases, and that satisfactory improvement is attained in approximately 60 per cent. For angina pectoris, the results were even better. Excellent results were obtained in 55.5 per cent and moderate improvement occurred in 28.12 per cent. They believe that the status at present is that good or satisfactory improvement occurs from total thyroidectomy in angina pectoris in 80 to 90 per cent of the cases.

It is desirable to keep the basal metabolic rate in these cases post-operatively at approximately -20 to -30.<sup>314</sup> The troublesome symptoms of myxedema do not become apparent as a general rule until the basal metabolic rate reaches -30. Small amounts of thyroid extract in those cases with definite myxedema (grain 0.1 to 0.5 daily) are sufficient for relieving the distressing symptoms and still keeping the metabolism at levels of approximately -25 to -30. Hertzler<sup>321</sup> looks askance at the subject. He says: "If this is kept in mind, one is forced to recognize the possibility that pronounced cardiac improvement is presumptive evidence that the thyroid gland was diseased and that the removal of it acted not so much as removing the whip as in removing toxic products which were injuring the heart."

The present status of the subject seems to be that there are certain cases of intractable heart disease that are definitely benefited by a total thyroidectomy so that these unfortunate individuals may return to work after such surgery. Likewise, the patient with angina pectoris in the medium between status anginosus and occasional sporadic attacks of pain may expect enough benefit from the operation to justify its being done. Let it be recorded here that Blumgart and Davis<sup>314</sup> report that massive doses of roentgen irradiation applied to the normal thyroid are ineffective in producing a persistent lowering of the basal metabolic rate.

#### MYXEDEMA

Some advances in our knowledge, especially of the therapy of myxedema, have been made recently, due in large part to the deliberate production of total thyroid deficiency for the treatment of heart disease. Thompson and his coworkers<sup>323</sup> attempt to show that thyroid extract from different animals gives the same result in myxedema if the iodine content is the same. Means<sup>149</sup> and Lerman<sup>324</sup> have given splendid discussions of the therapy in myxedema. Complete myxedema they regard as a metabolism -30 per cent below normal, or lower. They have studied the question of dosage of thyroid and find that in the completely myxedematous patient one-half grain of thyroid extract daily will maintain the basal metabolic rate of most cases about -20 per cent below zero. One grain maintains the rate at about -10 per cent,

one and one-half grains at about -5 per cent, and three grains at about zero or standard level. They do not believe it is necessary to raise the metabolic rate to zero. In their experience patients rarely have symptoms of myxedema when the basal metabolic rate is above -20. Blumgart and Davis<sup>314</sup> have found that amounts of thyroid extract varying between one-tenth and one-half grain daily are sufficient to relieve the individuals from distressing symptoms and still permit the metabolism to remain low. De Wesselow<sup>325</sup> advocates a small dose, one-half grain, of desiccated thyroid daily, increasing until a full maintenance dose of two or three grains daily is reached. Kena-Apajalahti,<sup>326</sup> studying the question of infantile myxedema, reiterates the already appreciated fact that the effect of thyroid therapy is not equally favorable in all cases.

#### THErapy FOR HYPERTHYROIDISM AND FOR GOITER

Surgery occupies in the clinics as well as in the literature the place of supremacy in the treatment of goiter, toxic or nontoxic. Though so far it has not made a significant impression, there is continually a repetition of attempts to cure goiter by other means. Such attempts fall in two categories: first and more commonly, into that of radiation therapy advocated by roentgenologists and radiotherapeutists; second, into a smaller and possibly even more commendable group of investigators attempting to supplant surgery and destructive means by some form of therapy that would correct the derangement that is responsible for the changes in the thyroid gland. All authors agree that x-ray or radium therapy in conjunction with surgery is the proper therapy for malignancy of the thyroid gland. For the treatment of toxic goiter or other types of goiter by irradiation therapy an appraisal of the value of the method may be obtained from the following quotations: Soiland, Costolow, and Meland<sup>327</sup> of 3,100 cases treated by irradiation therapy report 73 per cent clinically well, 16 per cent improved, 11 per cent unimproved. Goodwin and Smith<sup>328</sup> state that their objection to x-ray is that too much time is consumed. Hayer,<sup>329</sup> reporting on the treatment of 107 patients with thyrotoxicosis by x-ray, found 70.5 per cent improved, 9 per cent worse, 1.3 per cent dead. Engel<sup>330</sup> reports the rather uncommendable figures of a mortality of 13.6 per cent of surgically treated patients and 14.3 per cent for radiologically treated cases of Basedow's disease. Quigley<sup>331</sup> reported favorable results in approximately 70 per cent of patients with toxic goiters treated by radium therapy. In cases of toxic adenoma subsequent operation was required in approximately 50 per cent. Pareclier<sup>332</sup> states that when x-ray irradiation is beneficial the improvement occurs slowly so that at least six months must be allowed for the treatment. In at least 30 per cent of the cases no improvement occurred. Williams,<sup>333</sup> reporting on the x-ray treatment of goiter, stated that in his 200 cases an average of 10 treatments

were given in three and one-half months. Eighty and one-half per cent of the patients were definitely cured and 13.5 per cent were benefited. Menville<sup>334</sup> in a collected series totaling 10,541 patients found that radiation was followed by cure in 66.2 per cent of cases, marked improvement in 21 per cent, and recurrence in 8.45 per cent. Lüdin,<sup>335</sup> who states that the results of irradiation treatment in Basedow's disease are disputed chiefly by surgeons and that the chief disadvantage of irradiation is the greater frequency of recurrence, says that death following irradiation treatment in cases of patients considered too poor risks for operation occurs in spite of rather than because of irradiation. Dunhill<sup>336</sup> says that 140 of his patients who have had x-ray irradiation under favorable conditions came to operation eventually. Gallino<sup>337</sup> says that irradiation therapy for hyperthyroidism is contraindicated in subacute cases, cases with grave cardiac disease due to thyrotoxicosis, hyperthyroidism accompanied by marked pluriglandular disturbances, and forms of hyperthyroidism with nodular tumoral forms of enlargement of the thyroid gland, especially those with pressure symptoms. Other advocates of irradiation therapy for goiter are Allison,<sup>338</sup> Gerber,<sup>339</sup> Schteingart,<sup>340</sup> and Zweifel.<sup>341</sup> Gerber<sup>339</sup> says that it is not advisable to treat patients with high basal metabolic rates, patients with extremely large glands, and cases in which there are cardiac changes. Apparently in such a controversy existing between a minority of roentgenologists and a majority of surgeons the clinicians will be the unbiased observers. Suffice it to say that two outstanding investigators in that field, Marine<sup>45</sup> and Means,<sup>149</sup> believe that at present the best therapeutic program available for hyperthyroidism is subtotal thyroidectomy in the fully iodinated subject.

Attention has already been directed to attempts to establish some delicate test for indicating prognosis and for determining the operability of patients with toxic goiter. Seed<sup>343</sup> recently reemphasized certain clinical standards, especially that stationary or increasing weight indicates that the condition is improving and offers a good prognosis, that muscular strength is also a valuable index, and that a patient who is able to step up on a chair without assistance is able to withstand the operation.

Attention has already been called to attempts to relieve hyperthyroid crises by suprarenal extract (Pemberton<sup>49</sup>) and sodium chloride. Starr and Patton<sup>343</sup> have treated 13 cases of hyperthyroidism with extracts of pregnancy urine or theelin. It appears that the induction of a remission by extract of pregnancy urine is dependent upon normal ovarian functions. Remission occurred in 7 of the cases. In 6 cases the treatment failed entirely. Pemberton<sup>344</sup> and Jackson<sup>345</sup> have studied the problem of persistent and recurrent hyperthyroidism. Jackson<sup>345</sup> suggests for the prevention of both the elimination of focal

infection, strain, and occupational factors, permanent abstinence from coffee and other stimulants, and the long-continued use of iodine post-operatively.

The mortality for operation for goiter and the end-results of thyroidectomy for toxic and nontoxic goiter have been reported by many authors. A general résumé of the subject has been given in a splendid article by Boothby.<sup>137</sup> In general, the mortality by a number of surgeons is less than 1 per cent. Thompson, Taylor, and Meyer,<sup>347</sup> in a study between the preoperative condition of the patient and the operative mortality, say the operative mortality is partly due to the skill of the surgeon. This is obviously true, and to demonstrate that all the laurels do not belong to those centers dealing with large numbers of goiters, commendable are the reports of Horsley (Richmond),<sup>348</sup> who had no mortality in 183 consecutive thyroidectomies, and Drennen (Birmingham),<sup>349</sup> in whose series there was 1 death in 300 consecutive thyroidectomies. Goetsch,<sup>350</sup> studying the cause of mortality after thyroidectomy, found that approximately one-third of the patients died of hyperthyroidism. Maes and his coworkers<sup>222, 351</sup> have studied the problem of goiter in the negro and in the nonendemic area. Other studies on mortality and therapeutic failures have recently been made by Rogers<sup>352</sup> and Elkin.<sup>353</sup> Noehren<sup>354</sup> finds that the incidence of cure three months after operation is between 80 and 90 per cent following thyroidectomy. Coller and Potter<sup>355</sup> found rehabilitation in over 90 per cent of patients operated upon for exophthalmic goiter, 95 per cent respectively for cases with toxic adenoma and nontoxic goiter. Richter<sup>346</sup> reports successful results in thyrotoxicosis from operation in 98.4 per cent of cases. Unfortunately, certain reports, notably those of the foreign clinics (Engel,<sup>330</sup> Wallace and Wevill<sup>356</sup>), have high mortality rates from thyroidectomy.<sup>137</sup>

#### SPECIAL TECHNIQUES

The operation for thyroidectomy can be found described in numerous monographs and chapters and sections quoted and unquoted herein. Attention is called here to only a few unusual aspects of thyroidectomy. The operation for total thyroidectomy is adequately described by Berlin.<sup>309</sup> Emphasis is placed upon direct observation of the vocal cords for possible injury having occurred to the recurrent laryngeal nerve after the first lobectomy. Descriptions of operative technique for substernal and intrathoracic goiters have been given by Pemberton,<sup>357</sup> Lahey,<sup>358</sup> Clairmont.<sup>359</sup> Splitting the sternum is rarely necessary. The operations of Crile<sup>241</sup> for malignancy and of Lahey<sup>207</sup> for thyroiditis have been mentioned. Questionable are the procedures even recently advocated by Waterworth,<sup>360</sup> aspiration of cystic nodules with injection of a few drops of iodine, and Shaw,<sup>361</sup> cervical sympathectomy where symptoms are of such degree of severity as would contraindicate lobectomy of the thyroid.

## RECENT REVIEWS AND RÉSUMÉS

A number of commendable reviews have been made concerning the thyroid literature and the various phases of the thyroid problem within the last few years. Among many deserving special commendation are those of Marine,<sup>362-364</sup> Zimmerman,<sup>365</sup> Starr,<sup>366</sup> Boothby,<sup>137</sup> Means.<sup>149</sup> Of recent texts deserving attention there should be included Rienhoff,<sup>134</sup> Hertzler,<sup>191</sup> George Crile and his associates,<sup>367</sup> Eberts, Fitzgerald, and Silver,<sup>368</sup> Crotti,<sup>214</sup> Sloan,<sup>369</sup> and Means.<sup>370</sup>

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# Review of Recent Meetings

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## REVIEW OF THE SIXTH ANNUAL MEETING OF THE HARVEY CUSHING SOCIETY, PHILADELPHIA, MAY 6, 7, AND 8

JAMES C. WHITE, M.D., BOSTON, MASS.

*(From the Massachusetts General Hospital)*

THE sixth annual meeting of the Harvey Cushing Society was held at Philadelphia May 6, 7, and 8. Out of a series of over thirty papers which were presented by members of the Society and invited guests, the following have been abstracted:

Dr. John Fulton discussed the rôle of the cerebral cortex in the regulation of blood pressure. Very light ether anesthesia is most suitable for these experiments and the animal must be curarized to eliminate somatic motor responses. Under these circumstances Fulton was able to map out a rich representation of vasoconstrictor as well as vasodilator points in the cortex. These tend to overlap the somatic areas, i.e., autonomic representation is found only in those areas (motor and premotor) from which somatic movements are obtained in the uncurarized preparation. This arrangement doubtless enables somatic motor activity to be accompanied by appropriate autonomic adjustments. The vasodilator effect is brought out by splanchnicectomy, and the vasoconstrictor response by cutting the vagi (E. C. Hoff and Green). Barbiturates destroy these reactions, although they leave the somatic reactions of Area 4 intact. There are striking species differences in cortical representation of autonomic activity; e.g., in the dog there is contralateral vasodilation after removal of the frontal area, whereas, in macaques there is vasoconstriction.

Dr. Franklin Jelsma reported two cases of Schüller-Christian's disease. This condition is a form of lipid dystrophy in which xanthomatous deposits occur in the cranium and flat bones principally, occasionally in the long bones. According to the location of the deposits, certain symptoms will present. Pressure of the lipid material upon the region of the tuber cinereum may cause a diabetes insipidus; likewise exophthalmus may be present if the lipid material is in sufficient quantity in the retrobulbar region.

The disease is one of disturbed lipid metabolism with general systemic effects as well as the local effects caused by the lipid deposits. It may be grouped with the series of lipodystrophies which includes Gaucher's disease, Niemann-Pick's disease, and possibly Tay-Sach's disease. One of the cases reported was unusual in that the diabetes insipidus improved completely with roentgen therapy. In this case the blood cholesterol was 346 mm. per 100 c.c. of blood. Low fat diet and roentgen therapy seemed to offer the best results.

Dr. J. G. Lyerly reported two unusual instances of meningiomas situated posteriorly in the lateral ventricles. These apparently arose from the choroid plexus, which brings in some pia-arachnoid in its development. Ventriculograms in Lyerly's patients showed no hydrocephalus, and Bucy cited a case with similar findings, but Fincher and Spurling reported three cases in which there was extensive enlargement of the ventricle which was blocked by the tumor.

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Received for publication, June 17, 1937.

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# REVIEW OF THE THIRTY-EIGHTH ANNUAL MEETING OF THE AMERICAN PROCTOLOGIC SOCIETY

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*(From the Division of Proctology, Baylor University Department of Medicine)*

THE American Proctologic Society, organized in 1899 by the then outstanding proctologists of this country, has had uninterrupted yearly programs since that time. The Society's Fellowship list is limited to seventy-five, there being seven Honorary Fellows from Europe and France and several Associates from Canada and Cuba. The session in June of this year was held in Atlantic City under the presidency of Marion C. Pruitt, of Atlanta, who was succeeded by Harry Z. Hibshman, of Philadelphia.

The emphasized program features were two extended symposiums on anesthesia and colorectal malignancy, and the appearance in papers or discussions of several nonproctologists, including gastroenterologists (Crohn, of New York; Mackie, of New York), a pathologist (Lawrence Weld Smith, of Philadelphia) and a regional anesthetist (Lundy, of Rochester, Minn.).

Burrell Crohn presented his findings in connections with what he believes to be three separate entities, ileitis, right-sided colitis, and ordinary chronic ulcerative colitis which is a process beginning low in the left colon and extending upward. Both ileitis and right-sided colitis occur in young individuals, the average age of the patients being twenty-four years. Daniel Jones, of Boston, is under the impression that ileocolitis is chiefly a disease of the Jewish race, although Crohn doubts this because of reports of numerous cases from various parts of Europe; Crohn believes right-sided colitis to be nonspecific, usually beginning in the hepatic flexure or ascending colon with slow progressive advance in both directions. Although the prognosis under medical treatment is poor, the disease is much more amenable to surgical treatment than typical left colitis, providing extirpation of the diseased gut be carried out radically. Berg, of New York (reported by Crohn), after attempting segmental resection with fair results, now resects the entire colon to the sigmoid in three stages. In fifteen cases, one patient died in five weeks, two patients died considerably later; the twelve who survived are apparently cured.

The beneficial although perhaps temporary effects of long-continued cod liver oil instillations in chronic ulcerative colitis which were reported by Best, of Omaha, were corroborated by Rose Spiegel, working simultaneously in New York.

Various reports on neoplasms suggested that in some circumstances the accurate diagnosis of adenocarcinoma of the rectum may be clouded by the presence of benign intrarectal or pelvic infiltrating tumors (Daniels, of Los Angeles) such as endometriosis (Schofield and Bacon, of Philadelphia), neurofibroma (Keith, of Hartford), tuberculosis (Wheeler, Indianapolis), adenomas (Martin, Louisville, and Scarborough, San Francisco), and diverticulum (Freund, New York City); or by infiltration of the bowel by extrarectal malignancy such as ovarian carcinoma (Kleekner, of Allentown) or sarcoma (Werner, Philadelphia).

The therapy of rectal cancer is apparently not yet so standardized that discussion is unnecessary. In the symposium on cancer, the value of radon implants

Received for publication, June 24, 1937.

Dr. Frederiek Schreiber pointed out the dangers to the central nervous system of the increasing use of heavy sedation to promote painless labor. He has studied the birth history of twenty cases given multiple heavy doses of scopolamine or barbiturates in which the outlook for spontaneous delivery was good, but the child was born with cerebral damage.

The type of drug is not as important as the anoxemia induced. Such babies are born blue. They are hard to resuscitate and some die. Both mothers and babies may develop evidence of cerebral injury. The babies may show spastic paralysis and severe cortical atrophy on encephalography. Secondary to these organic changes, mental deterioration and epilepsy may result. Some of the mothers have shown mental changes. They become jittery and cry easily. Occasionally the evidence of injury to the higher cerebral functions has been definitely increased by multiple deliveries under heavy sedation with an accompanying high grade of anoxemia.

The incidence of surgical interference in the normal course of labor has risen with the use of analgesia. Rapid mechanical molding of the head with forceps or version reproduces the dangers of precipitate delivery. A blue baby, born of a drugged mother, is potentially a spastic, an epileptic, or an idiot.

Dr. Tracy J. Putnam and Dr. Donald Munro presented reports of three patients who had an unusual postoperative reaction to high anterolateral or anterior cordotomies. All of these were in good condition immediately after operation, but subsequently developed profound mental changes (confusion, delirium, and hallucinations) leading to death within a week or two. High cord tumors and cervical fractures have caused a similar condition. This progressive confusional syndrome is probably due to anoxemia of the brain. The oxygen content of the arterial blood drops to 12 or 13 per cent in some cases, close to levels where symptoms are known to develop. In others, sluggish circulation and anemia add to the disturbance. The picture resembles mountain sickness or decompensation, and is most common in older people. Anemia and sedatives increase it. The treatment recommended is transfusion and the use of a respirator as indicated. Anesthetics, sedatives such as morphine and the barbiturates, and carbon dioxide inhalations should be avoided.

Dr. W. McK. Craig presented nine cases of intracerebral hemorrhage in which operation had been carried out. In reviewing the literature, he stated that Dr. Cushing was probably the first surgeon to operate for subcortical hemorrhage. It was interesting to note that trauma played a definite rôle in two of the nine cases, was suggested in a third, was suspected in a fourth, and in a fifth a subcortical hemorrhage was found twelve years after an injury to the head. In two other cases, the cerebral hemorrhages followed emotional stress, and in one case the hemorrhage was associated with rheumatic heart disease and endocarditis.

Craig further stated that intracerebral hemorrhages have been attributed to faulty structure of the arterioles or venules within the substance of the brain, with subsequent rupture of small sacculations. In view of the fact that the hemorrhages did not result in extensive extravasation, he suggested that they were of venous rather than arterial origin. A history of trauma was always suggestive of hemorrhage and yet in the cases in which encephalograms or ventriculograms were made, they did not reveal shadows or defects characteristic of hemorrhage. A diagnosis of subcortical hemorrhage was established at the time of operation, and craniotomy and incision of the cortex, drainage, and removal of the residual clots was the treatment carried out in all cases. A census of the Society yielded twenty-seven such cases.

The symptoms in all cases consisted of those of an expanding intracranial lesion. Headache, choked discs, convulsions, and hemiparesis were prominent clinical manifestations of intracerebral hemorrhage.

## REVIEW OF THE MEETING OF THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS

MORTON F. MASON, PH.D., NASHVILLE, TENN.

(From the Department of Biochemistry, Vanderbilt University)

**THE Effect of Epinephrine Injected Intravenously at a Constant Rate in Normal and Hypertensive Cases**, Alfred E. Koehler, Norman Marsh, and Elsie Hill (Santa Barbara Cottage Hospital and the Sansum Clinic, Santa Barbara).—Epinephrine 1:50,000 was administered intravenously in patients at a constant rate of 2 mg. per hour. In normal patients there was a constant sustained rise of systolic blood pressure. The diastolic pressure also rose at first, but later tended to drop below the control period. The basal rate increased about 30 per cent and there were increases in blood sugar and lactic acid. Almost immediately after cessation of injection, both systolic and diastolic pressures dropped markedly below their values during the control period. In patients with essential hypertension, the lactic acid increase was not as great. The average blood pressure rise was consistently greater than in the case of normal patients and the drop and duration of drop of blood pressure after cessation of injection were greatly increased. There was no evidence that myocardial failure was related to the drop in pressures following injection.

**The Prolongation of Insulin Action**, A. M. Fisher and D. A. Scott (Connaught Laboratories, University of Toronto).—Incubated preparations containing spermine, zinc, and insulin produce prolonged hypoglycemia in rabbits and dogs. A preparation from beef blood has also been found to modify (prolong) ordinary insulin action. Zinc is an essential constituent of the various modified insulin preparations.

**Some Observations on the Source of Urinary Cystine in Cystinuria**, E. Brand, R. J. Bloch, and G. F. Cahill (Department of Chemistry, New York Psychiatric Institute and Hospital, and Squier Urological Clinic, Presbyterian Hospital, New York).—Observations on the metabolism of casein and lactalbumin in a case of cystinuria further support the hypothesis that the urinary cystine in patients with this error of metabolism is derived, not from cystine of dietary protein, but from methionine.

**A Volumetric Method for the Determination of Acacia in Serum, Lymph, and Urine**, Marschelle H. Power (Division of Biochemistry, the Mayo Foundation, Rochester, Minn.).—A method was described permitting the accurate determination of acacia in serum, lymph, and urine. The neacin is precipitated from trichloroacetic acid filtrates of serum or lymph, or from urine by treatment with acetone. The precipitated acacia is oxidized with chromic acid and the excess chromic acid estimated iodometrically. For details of the method, the original paper should be consulted.

**Quantitative Determination of Prothrombin**, Armand J. Quick and Madeline Leu (Department of Pharmacology, Marquette University School of Medicine, Milwaukee).—The rate of coagulation is assumed to be a function of the concentration of thrombin which in turn is proportional to the concentration of prothrombin when an excess of thromboplastin substance is present with ade-

Received for publication, May 17, 1937.

and local removal in those unsuitable for surgery was mentioned by Binkley of New York; desiccation was advocated in suitable cases by E. G. Martin, of Detroit and Buie of Rochester, Minn., while Lynch and Hamilton, of New York City, while advocating radical surgery, had a kind word to say for the periaecal anus.

The majority of those answering Cartwright's questionnaire (Fort Wayne) favored radical rather than temporizing measures in strangulated hemorrhoids. Yeomans, of New York City, discussed the anatomic relations and repair of an infrequent type of hernia through the levator ani muscle, and Hibshman, of Philadelphia, advocated wide and early drainage of suprlevator abscesses through the posterior ischiorectal space.

Woolf, of San Francisco, reflected what I believe to be the majority opinion of American proctologists when insisted that proctology is a surgical specialty and that it is essential that those entering the field have surgical training that includes the abdominal zone.

The transactions of the Society are published in a single annual volume.

**Physiologic Effects of Phenol-Contaminated Drinking Waters, V. G. Heller and Lee Pursell** (Oklahoma Agricultural Experiment Station, Stillwater).—The toxicity of long-continued consumption by rats of water containing phenol was investigated. A water supply containing as much as 0.8 per cent phenol does not interfere with growth reproduction and lactation. Involved nutritional studies indicate that normal metabolism is not disturbed until the contamination of water with phenol approaches one per cent. The phenol is readily detoxified and the conjugated compounds appear in the urine.

**The Effects of Minute Amounts of Lead on the Animal Organism, M. K. Horwitt and George R. Cowgill** (Laboratory of Physiological Chemistry, Yale University School of Medicine, New Haven).—The point of view that small amounts of lead in the diet are deleterious was subjected to experimental test using rats. Growth was not affected when diets containing up to 100 mg. per kilogram of lead were fed. No anemia developed nor was "stippling" observed. In three successive generations reproduction was normal. Many experimental diets in common use in various laboratories were found to contain more than the present government tolerance of 2.6 mg. lead per kilogram, none of these diets having any untoward effects on the animals receiving them. The dithizone micro-method was employed in determining lead.



quate calcium ions. The determination is performed as follows: 9 vol. of blood mixed with 1 vol. of 0.1 M sodium oxalate are centrifuged and the plasma separated. A small test tube containing 0.1 c.c. of the plasma mixed with 0.1 c.c. of thromboplastic substance (an emulsion prepared from rabbit brain) is kept at 40° in a water-bath; 0.1 c.c. of 0.025 M calcium chloride is quickly added and the time required for clotting noted. The times are quite constant for normal animals of the same species, but there are species differences. The actual observed time varies somewhat with different thromboplastin preparations.

**Fatty Livers in Geese, Produced by Overfeeding, Eunice Flock, Jesse L. Bollman, H. R. Hester, and Frank C. Mann** (Division of Experimental Medicine, the Mayo Foundation, Rochester, Minn.).—Fatty livers were produced in geese by continued overfeeding with a high carbohydrate diet during the day. These livers contained up to 15 per cent fatty acids. When night feeding was also employed, values as high as 48 per cent were found. This fat was more saturated than depot fat. The water content of the livers diminished with increasing fat content, but the glycogen contents varied. Large increases in depot fat were observed.

**Further Observations of the Effect of Parenteral Injection of Amino Acids and Related Substances Upon Creatine Formation and Storage in Rats, H. H. Beard, T. S. Boggess, and P. Pizzolato** (Department of Biochemistry, Louisiana State University Medical Center, New Orleans).—A large number of dietary experiments on rats support the contention that urea and glycine as such, or arising as intermediaries in amino acid metabolism, are the precursors of creatine.

**The Dietary Production of Parathyroid Hypertrophy in Rabbits, E. J. Baumann and D. B. Sprinson** (Laboratory Division, Montefiore Hospital, New York).—Rabbits fed on a diet of carrots and oats develop parathyroid hypertrophy, the gland weights increasing as much as 400 per cent. The Ca:P ratio of this diet is 0.5 in contrast to a ratio of 4 in the stock diet. The serum calcium remains normal, the inorganic phosphate is somewhat depressed, and an increase in circulating parathormone is demonstrable (Hamilton's test). In adult rabbits the serum phosphatase content is markedly depressed.

**The Effect of Vitamin B<sub>1</sub> on the Respiratory Quotient, Dorothy V. Whipple and Charles F. Church** (Department of Pediatrics, School of Medicine, University of Pennsylvania, Philadelphia).—When vitamin B<sub>1</sub> deficient rats were given glucose subcutaneously, the respiratory quotient remained below 1, while those of isocaloric controls receiving the vitamin were above unity. Crystalline vitamin B<sub>1</sub> raised the respiratory quotients of animals with severe beriberi symptoms to values also above unity. The observations were in harmony with the authors' hypothesis that vitamin B<sub>1</sub> must be present in the metabolic mixture to permit synthesis of fat from carbohydrate in the animal body.

**The Toxicity of Calciferol for Rabbits, Arthur M. Hartman** (Division of Nutrition and Physiology, Bureau of Dairy Industry, United States Department of Agriculture, Beltsville).—Young rabbits placed on diet of natural foods were administered calciferol by mouth in various doses six days per week. The calciferol was dissolved in cottonseed oil. When the diet contained alfalfa of good quality, the toxicity of the calciferol was not in evidence at as low levels of dosage as when a poor quality of alfalfa was used. The toxic effects were observed more frequently in males than in females. Autopsies disclosed degenerative changes including metastatic calcification in the aorta and kidneys of these animals on dosages of calciferol as small as 0.02 mg. per day. In experiments prolonged over several months dosages not immediately toxic produced these changes. The calciferol was pure according to spectrophotometric tests.

that, from the standpoint of pathologic physiology, Addisonian pernicious anemia and pernicious anemia of pregnancy reflect disturbances in essentially identical mechanisms.

#### Chronic Hepatogenic Hypoglycemia Due to Ascending Cholangiolitis, With Recovery Following Cholecystectomy

Jerome W. Conn (introduced by Raphael Isaacs), University of Michigan Medical School

The literature reveals no report of a case of chronic hepatogenic hypoglycemia due to ascending infectious hepatitis. An extensive study of the metabolism in such a case was made before and after the removal of the source of the ascending hepatitis. A remarkable recovery of the previously impaired glycogenic function of the liver was observed.

Before cholecystectomy, frequent episodes of coma occurred spontaneously, with the blood sugar at such times ranging between 14 and 20 mg. per hundred cubic centimeters. Dextrose tolerance tests suggested that the hypoglycemia was due to deficient hepatic glycogenesis rather than to excessive production of endogenous insulin. Indirect calorimetry showed that while the blood sugar was dropping to hypoglycemic levels the oxidation of dextrose was normal. Numerous types of tests consistently revealed deficient hepatic function.

Exploratory laparotomy revealed a grossly normal pancreas. Biopsy of the liver showed active chronic cholangiolitis and biliary cirrhosis.

After cholecystectomy, gradual improvement occurred until virtual recovery was attained. No spontaneous hypoglycemic attack has occurred since operation. Dextrose tolerance tests are essentially normal. All tests show normal hepatic function. Indirect calorimetry still reveals normal oxidation of dextrose.

This study indicates that chronic infection of the biliary tract may so injure the glycogenic and glycogenolytic functions of the liver that severe spontaneous hypoglycemia results.

#### Parenteral Protein in Pneumonias

Clyde Brooks, Louisiana State University Medical Center, New Orleans

In 1,200 cases of pneumonia, including all forms and patients of all ages, the best routine treatment of the medical center was used, including a hygienic regimen, nursing, medication, and surgical intervention when indicated.

One half of the patients were used as controls; the other half were treated by the parenteral administration of deuteroproteose.

The results show that among the controls the death rate was 39 per cent for lobar pneumonia and 32 per cent for bronchopneumonia. The death rate in the cases in which treatment was by deuteroproteose was 10 per cent for lobar pneumonia and 9 per cent for bronchopneumonia.

The results are encouraging, if not conclusive. They indicate that the parenteral use of deuteroproteose reduces the death rates for both lobar and bronchial pneumonia.

#### Effect of Artificial Fever on Experimental Rabies

F. D. McCrea (introduced by Douglas H. Sprunt) and Harold M. Horack (introduced by Douglas H. Sprunt), Duke University

Rabbits were inoculated intracerebrally with fixed rabies virus. Then, by exposure of the animals to radiant heat, their body temperatures were elevated and maintained between 41.2° and 41.8° C. (106.1° and 107.2° F.). Unheated controls were checked against each heated group.

# REVIEW OF THE MEETING OF THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

MORTON F. MASON, PH.D., NASHVILLE, TENN.

(From the Department of Biochemistry, Vanderbilt University)

## ABSTRACTS OF PAPERS PRESENTED\*

### Correlation of Serum Iron, Bone Marrow, and Blood Cell Changes Following Specific Therapy in the Macrocytic Anemias

Carl V. Moore (by invitation) and Charles A. Doan, Ohio State University

The observation has been made that the nonhemoglobinous iron of the serum is higher than normal in the relapse phase of pernicious anemia. Beginning within twenty-four hours after the institution of adequate liver therapy, this iron fraction of the blood falls precipitously to a level that is below the normal range. The change thus precedes by three or four days the reticulocytosis that follows therapy.

Consequently, in order that the reequilibration in the serum iron could be more adequately understood with reference to the altered physiology of the erythropoietic tissue, serial supravital differential cell counts of sternal marrow, obtained by the puncture technique, were made for two patients, with pernicious anemia both before and after the commencement of specific therapy. Blood for an analysis as to iron content was drawn within a few minutes after the sternal puncture was made.

Within twenty-four hours after the administration of liver began, there was evident in the bone marrow a definite shift to the right in the level of the erythrocytic maturation. Megaloblasts were fewer, and mitotic figures were markedly increased. During the subsequent forty-eight hours a transition from a predominantly erythroblastic to a predominantly normoblastic marrow, with resultant discharge of reticulated red cells into the peripheral blood, was accomplished. The fall in serum iron closely paralleled the cytologic changes, reaching its greatest depression at the time of maximum delivery of erythrocytes from the bone marrow (the reticulocyte peak in the peripheral blood). These findings are interpreted as offering further evidence for the concept of serum iron as iron in transportation. It is considered that the decrease in serum iron occurred and persisted during these experiments for two reasons: (1) After the institution of liver therapy any increase in hemolytic activity promptly subsided; and (2) with the increase in synthesis of hemoglobin coincident with the reinstitution of normal maturation, the iron being transported in the serum was withdrawn from the blood by the bone marrow and utilized at a more rapid rate than normal. The low serum iron under these conditions does not reflect inadequate storage of iron in the body depots.

In addition to hemoglobin iron and serum iron, a third form of blood iron has been described: "ensily split-off iron." It is possibly, but not as yet certainly, of nonhemoglobinous origin. This third fraction remained at a fairly constant level during the changes described.

One of the two patients studied had Addisonian pernicious anemia; the other had pernicious anemia of pregnancy, in which the disease had been produced primarily by a deficiency in a dietary extrinsic factor. The responses in cytologic and serum iron in the two patients were identical and constitute further evidence

Received for publication, May 17, 1937.

\*Authors' abstracts.

In cats it was found that ligation of the common bile duct does not cause an appreciable rise in the blood phosphatase, but that the serums of these animals can be activated by cevitic acid in the same manner as the serums of the dogs or human serums.

These experiments indicate that in complete biliary obstruction in the dog the increase in the value for circulating phosphatase is due to an increase in the activity of the phosphatase and not to an increase in its amount. They also indicate that in dogs with experimental biliary fistulas an increase in circulating phosphatase occurs without obstructive jaundice. It seems that the diagnostic value of an increase in serum phosphatase in certain pathologic conditions is limited.

The experimental animals were divided into five groups according to the number of hours of exposure to heat and the time of exposure as follows: (1) seven or twelve hours the day of inoculation; (2) six, seven, or twelve hours twenty-four hours after inoculation; (3) seven hours the same day and seven hours forty-eight hours after inoculation; (4) twelve hours the same day and twelve hours forty-eight hours after inoculation; (5) twelve hours the same day and twelve hours forty-eight hours after inoculation.

The first four groups received 0.2 c.c. of virus diluted 1:200; the fifth group, 0.2 c.c. of virus diluted 1:100.

All controls and heated animals in groups 1, 2, and 3 died of rabies within from seven to fourteen days. In group 4, all nine controls died of rabies; of the fifteen heated animals, three died during the heating period and five of causes other than rabies; seven survived and by February 13, 1937, had outlived their corresponding controls sixty-two, seventy-six, ninety, one hundred and two and two hundred and twenty days. Two controls and four heated animals comprising group 5 died of rabies. Whether this is significant we do not know.

Forty white rats were inoculated intracerebrally with 0.05 c.c. of virus diluted 1:50 and on up to 1:400. In all the rats symptoms typical of rabies developed, followed by death. Blood serum from two surviving rabbits was mixed with virus, making dilutions of the latter varying from 1:50 to 1:400; these were incubated two hours at 37.5° C. and inoculated intracerebrally into thirty-six rats. All died with symptoms typical of rabies. Like dilutions were inoculated intracerebrally into eight rabbits, which also died with paralyses typical of rabies. Serum from surviving rabbits apparently has no protective action and seems to transfer no immunity.

#### Values of Phosphatase in the Serum and Bile of Dogs With Experimental Biliary Fistulas and in Dogs With Complete Biliary Obstruction

Siegfried Thannhauser (by invitation), Stephen Maddock, M. Reichel  
(by invitation), and Jerome F. Grattan (by invitation),  
Boston City Hospital

Experience with increasing and decreasing phosphatase activity and with the splitting of sphingomyelins by phosphatase suggested the possibility of activating the phosphatase of the blood serum *in vitro*. It was found that cevitamic acid (introduced as ascorbic acid) in appropriate concentrations would activate serum phosphatase. The activation is proportional to the concentration of cevitamic acid within certain limits and bears no relation to time. The optimum pH is identical with that of normal phosphatase activity. As it was known that following complete biliary obstruction a marked rise in serum phosphatase occurred, the common bile duct was ligated in series of dogs, and studies were made of the serum phosphatase. It was found that after ligation the phosphatase of these serums rose from about 2 to about 100 Bodansky units in three weeks. These same serums were activated with 5 mg. of cevitamic acid per tenth cubic centimeter. The activity of all the serums rose to about 150 Bodansky units regardless of the initial value prior to activation, so that an almost uniform maximum activity was found after the addition of cevitamic acid, which was independent of the progressive increase in the concentration of phosphatase produced by biliary obstruction.

Dogs with total biliary fistulas were also studied, and it was found that the serum phosphatase rose to about ten times the normal levels. Cevitamic acid was effective in the serums of these dogs in the same manner as already described. The values of the phosphatase in the bile coming from the fistulas showed, in contrast to the values for that in the serum, almost complete activation.

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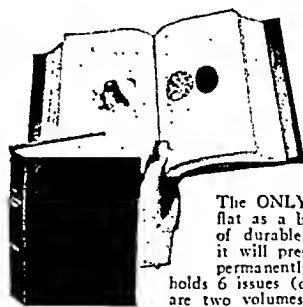
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## Book Review

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**Medical Urology.** By Irvin S. Koll. Pp. 431, with 92 text illustrations and 6 color plates. St. Louis, 1937, The C. V. Mosby Company. \$5.

The author has prepared this volume . . . "to present the subject in such a manner as to be of practical value to the general physician and an aid to the medical student." He adheres closely to this purpose throughout and has succeeded in presenting a very good synopsis of urologic principles. The book is profusely illustrated. Where there is indication for further study of the material in any chapter, extensive bibliographical references are appended.

Gonorrhea and its complications are discussed with a view to establishing a conservative, though inadequate, system of treatment. In these chapters the author has been particularly careful in stating the reasons underlying the methods which are suggested, so that the practitioner or student can proceed to their application in a rational manner. That part of the book which is devoted to consideration of the major surgical problems in urology contains few details of treatment. There is no pretense at description of operations. Cystoscopy is considered principally from the standpoint of its diagnostic value. In the chapter on the surgical diseases of the prostate, the author has wisely confined his remarks to the principles of diagnosis and preoperative care. The reader is neither subjected to a technical description of the different methods for surgical attack on the prostate nor is he drawn into controversy regarding the relative merits of prostatectomy and transurethral resection.

This book can be only of passing interest to the specialist in urology, but it provides both the general physician and the medical student with a useful practical handbook for guidance.

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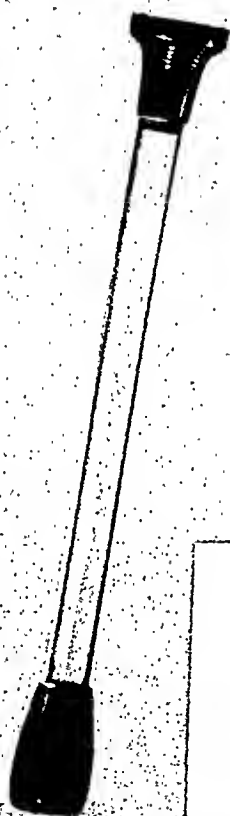
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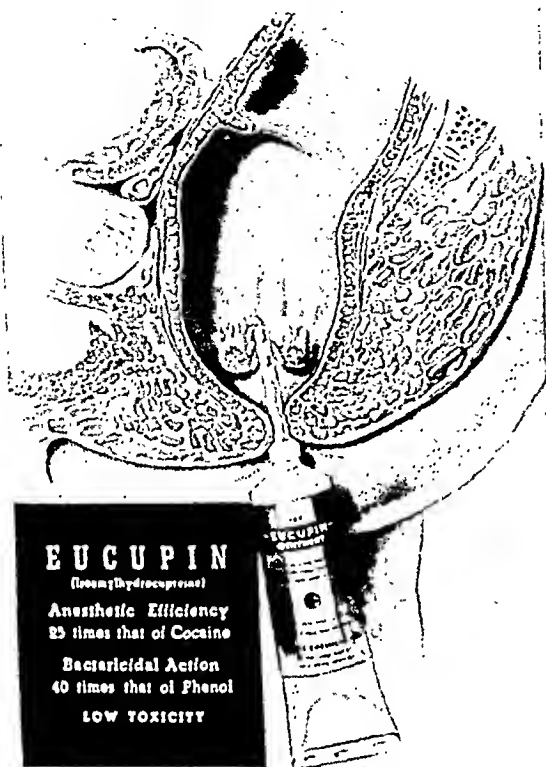
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Tablets Sulfanilamide, Lilly, 5 grains (0.325 Gm.) are supplied in packages of 40, 100, and 500.

**ELI LILLY AND COMPANY**  
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